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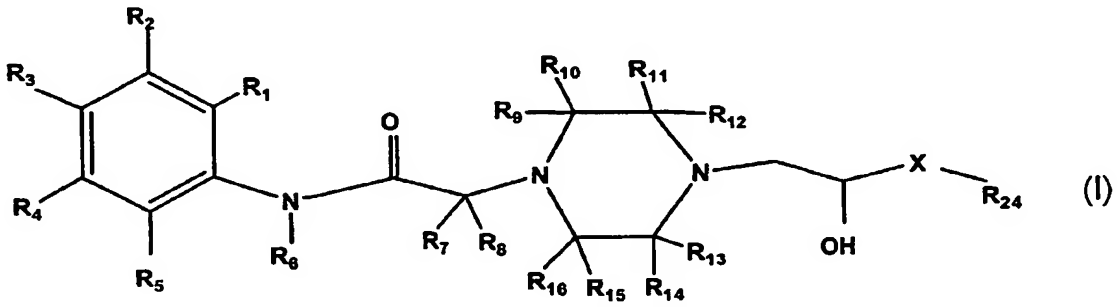
(54) Title: SUBSTITUTED PIPERAZINE COMPOUNDS



(I)

(57) Abstract: Novel compounds of the general formula (I) and pharmaceutically acceptable acid addition salts thereof, wherein the compounds are useful in therapy to protect skeletal muscles against damage resulting from trauma or to protect skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, in the treatment of cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction.

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TITLE: SUBSTITUTED PIPERAZINE COMPOUNDS

BACKGROUND OF THE INVENTION

This application claims priority to U.S. Patent Application Nos. 60/184182 filed on February 22, 2000, 60/184457, filed on February 22, 2000, 60/206396, filed on May 23, 2000, 60/184306 filed on February 22, 2000, and to U.S. Patent Application 60/209262 filed on June 5, 2000, the specification of which is incorporated herein by reference.

1. Field of the Invention

The present invention is concerned with substituted piperazine compounds, therapeutic dosage forms including one or more of the compounds, and methods for treating diseases in mammals, and in particular, in a human in a therapy selected from the group including protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, and to treat cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction.

2. Description of the Art

U.S Patent No. 4,567,264, the specification of which is incorporated herein by reference, discloses a class of substituted piperazine compounds that includes a compound known as ranolazine, (±)-N- (2,6-dimethylphenyl)-4-[2-hydroxy-3- (2-methoxyphenoxy)-propyl]-1-piperazineacetamide, and its pharmaceutically acceptable salts, and their use in the treatment of cardiovascular diseases, including arrhythmias, variant and exercise-induced angina, and myocardial infarction.

U.S. Patent No. 5,506,229, which is incorporated herein by reference, discloses the use of ranolazine and its pharmaceutically acceptable salts and esters for the treatment of tissues experiencing a physical or chemical insult, including cardioplegia, hypoxic or reperfusion injury to cardiac or skeletal muscle or brain tissue, and for use in transplants. In particular, ranolazine is particularly useful for treating arrhythmias, variant and exercise-induced angina, and myocardial infarction by partially inhibiting cardiac fatty acid oxidation. Conventional oral and parenteral ranolazine formulations are disclosed, including controlled release formulations. In particular, Example 7D of U.S. Patent No. 5,506,229 describes a controlled

release formulation in capsule form comprising microspheres of ranolazine and microcrystalline cellulose coated with release controlling polymers.

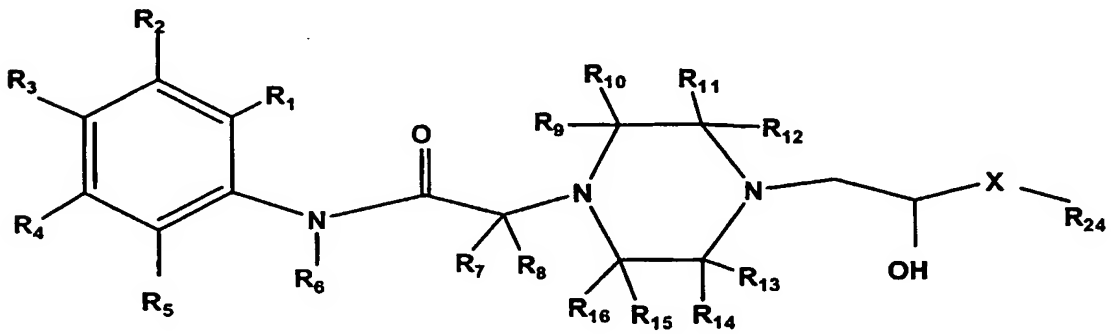
Despite the important discovery that ranolazine is a very useful cardiac therapeutic agent, there remains a need for compounds that are partial fatty acid oxidation inhibitors that have a half-life greater than ranolazine and that have activities as least similar to ranolazine.

SUMMARY OF THE INVENTION

This invention includes novel substituted piperazine compounds that are partial fatty acid oxidation inhibitors with good therapeutic half-lives.

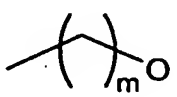
This invention also includes novel substituted piperazine compounds that can be administered to a mammal to protect skeletal muscles against damage resulting from trauma, to protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, and to treat cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction.

This invention includes a class of substituted piperazine compounds having the following formula:



wherein X is selected from the group consisting of:

and



wherein m = 1 or 2 or 3;

R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22} , wherein R_2 and R_3 may join together to form a fused ring system having from three to four carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-;

R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen and C_{1-15} alkyl;

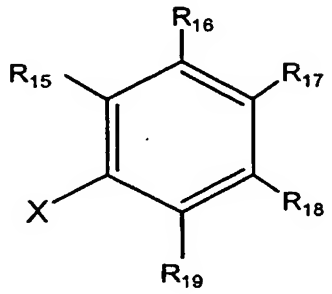
R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, CO_2R_{23}, $CON(R_{23})_2$, C_{1-4} alkyl, and aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ and aryl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a bridging ring system having from 1 to 4 carbon atoms and wherein R_9 and R_{10} or R_{11} and R_{12} or R_{13} and R_{14} or R_{15} and R_{16} may join to form a bridging ring system having from 1 to 5 carbon atoms.

R_{22} is selected from the group consisting of C_{1-15} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, and heteroaryl;

R_{23} is selected from the group consisting of H, C_{1-15} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl, CN, -O-C_{1-6} alkyl, and CF_3; and

R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to three substituents selected from the group consisting of halo, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, C_{1-2} alkyl, and aryl wherein the optional aryl substituent is

optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl, and

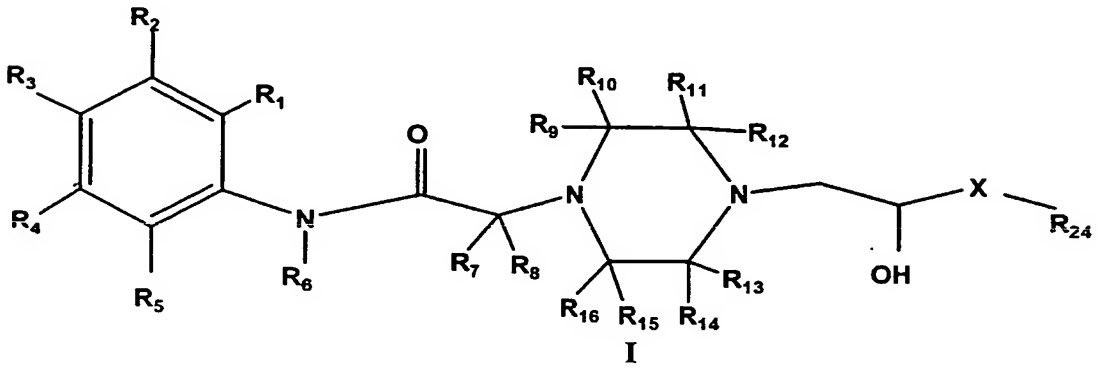


wherein R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22}.

In yet another embodiment, this invention is a method for administering one or more composition of this invention to a mammal in a treatment selected from the group consisting of protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, and to treat cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction.

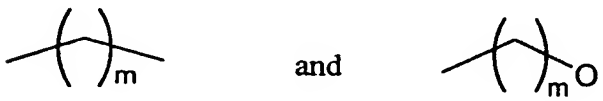
DETAILED DESCRIPTION OF THE INVENTION

This invention includes a class of substituted piperazine compounds having the following formula:



I

wherein X is selected from the group consisting of:



wherein m = 1 or 2 or 3;

R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22} , wherein R_2 and R_3 may join together to form a fused ring system having from three to four carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-;

R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen and $C_{1\text{-}15}$ alkyl;

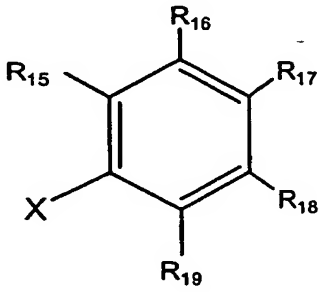
R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, CO_2R_{23}, $CON(R_{23})_2$, $C_{1\text{-}4}$ alkyl, and aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ and aryl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a bridging ring system

having from 1 to 4 carbon atoms and wherein R_9 and R_{10} or R_{11} and R_{12} or R_{13} and R_{14} or R_{15} and R_{16} may join to form a bridging ring system having from 1 to 5 carbon atoms;

R_{22} is selected from the group consisting of C_{1-15} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, and heteroaryl;

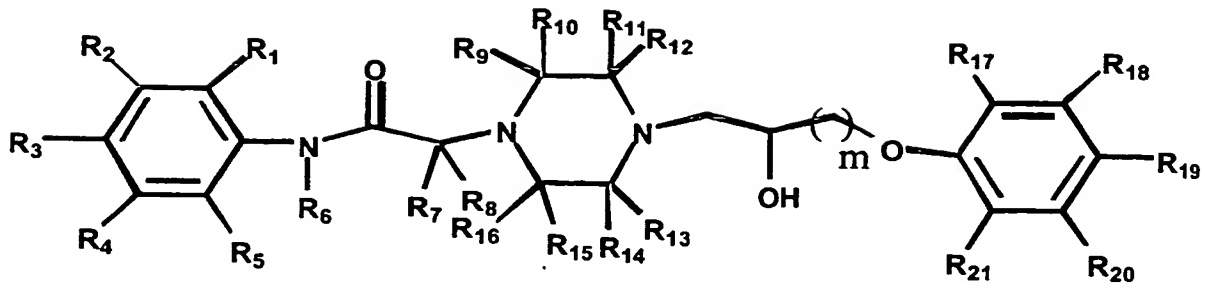
R_{23} is selected from the group consisting of H, C_{1-15} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl, CN, -O-C_{1-6} alkyl, and CF_3; and

R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to three substituents selected from the group consisting of halo, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, C_{1-2} alkyl, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl and



wherein R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22}.

This invention also includes a subset of the class of substituted piperazine compounds identified in Formula I above having the following Formula (IA):



IA

wherein m = 1, 2;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-4} alkyl and wherein R^{22} is a C_{1-3} alkyl;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and C_{1-3} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl, or R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a bridging ring system wherein the two R groups together comprise of from 1 to 4 carbon atoms with the proviso that R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are not all simultaneously hydrogen.

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR^{22}, $S(O)R^{22}$, SO_2R^{22}, $SON(R^{22})_2$, $CON(R^{22})_2$, C_{1-4} alkyl wherein R^{22} is C_{1-3} alkyl, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$.

In more preferred compounds of Formula IA, R^1, R^2, R^3, R^4 and R^5 are each selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-4} alkyl where R^{22} is a C_{1-3} alkyl; R^6 is selected from hydrogen and methyl; R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from hydrogen and methyl or R^9 and R^{10} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl with the proviso that R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are not all simultaneously hydrogen.; R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22}, C_{1-3} alkyl wherein R^{22} is C_{1-3} alkyl, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$.

In still more preferred compounds of Formula IA, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of methyl and hydrogen; R^9, R^{10}, R^{11},

R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from hydrogen and methyl or R^9 and R^{10} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl with the proviso that R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are not all simultaneously hydrogen; R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} wherein R^{22} is methyl, methyl, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$

In an even more preferred compounds of Formula IA, R^1 and R^5 are each methyl; R^2, R^3, R^4, R^6, R^7, R^8 are each hydrogen; R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from hydrogen and methyl or R^9 and R^{10} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl with the proviso that R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are not all simultaneously hydrogen; R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, methyl, OR^{22} wherein R^{22} is methyl, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$.

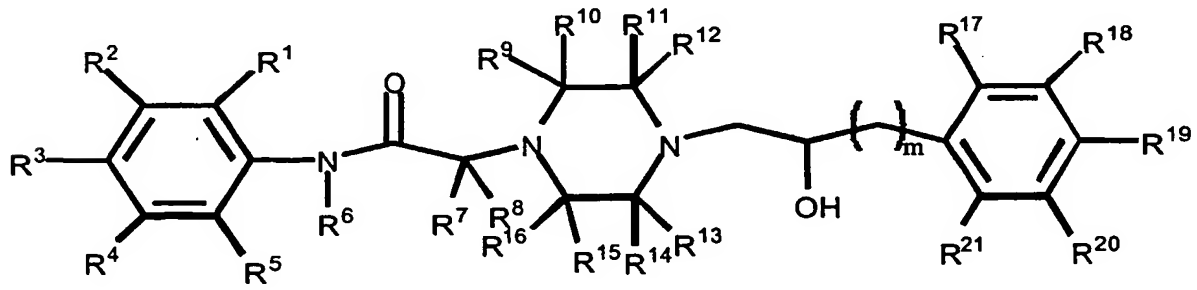
In still more preferred compounds of Formula IA, R^1 and R^5 are each methyl; R^2, R^3, R^4, R^6, R^7, R^8 are each hydrogen; R^9, R^{10} are selected from hydrogen, methyl, or may together form a carbonyl; R^{11} and R^{12} are selected from hydrogen and methyl; R^{13} and R^{14} are selected from hydrogen and methyl or may together form a carbonyl; R^{15} and R^{16} are hydrogen with the proviso that R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are not all simultaneously hydrogen; R^{17} is selected from the group consisting of hydrogen, chloro, fluoro or methoxy; R^{18} and R^{19} are each selected from the group consisting of hydrogen or methoxy, or R^{18} and R^{19} may together form $-OCH_2O-$, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, R^{20} is hydrogen; and R^{21} is selected from hydrogen or chloro.

Most preferably, the substituted piperazine compounds of Formula IA are selected from the group consisting of N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3-oxopiperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3,5-dimethylpiperazinyl}acetamide; 2-{(5S,2R)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-2,5-dimethylpiperazinyl}-N-(2,6-dimethylphenyl)acetamide, 2-{2,5-diaza-5-[2-hydroxy-3-(2-methoxyphenoxy)propyl]bicyclo[4.4.0]dec-2-yl}-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3-oxopiperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3,3-dimethylpiperazinyl}acetamide, 2-{5-[(2S)-2-hydroxy-3-(2-methoxyphenoxy)propyl](1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl}-N-(2,6-

dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-4-(2-methoxyphenoxy)butyl]- piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[4-(4-fluorophenoxy)-2-hydroxybutyl]- piperazinyl}acetamide, 2-(4-{4-[4-(tert-butyl)phenoxy]-2-hydroxybutyl}piperazinyl)-N-(2,6-dimethylphenyl) acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-4-(4-phenylphenoxy)butyl] piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-4-(4-methoxyphenoxy)butyl]- piperazinyl}acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2,6-dimethylphenyl)acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2,6-dichlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-sulfamoylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(5-methoxy-3-(trifluoromethyl)phenyl]acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-indan-5-ylacetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-naphthylacetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-chloronaphthyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2-pyrrolylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-phenylacetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2-chlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2-chloro-4-methylphenyl)acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[2-(1-methylvinyl)phenyl] acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2-methylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[6-methyl-2-(methylethyl)phenyl] acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3-methylthiophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-chloro-2-methoxy-5-methylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[4-(dimethylamino) phenyl] acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2,4-dimethoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3,4-dichlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-chlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3-chlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3,5-dichlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-

(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-methoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-methylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3-methylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-fluorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-cyanophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-acetylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2-methoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[4-(trifluoromethyl)phenyl] acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[4-chloro-3-(trifluoromethyl)phenyl] acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3,5-dimethoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-morpholin-4-ylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3-fluoro-4-methoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3,4,5-trimethoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3,4-dimethoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-chloro-2-fluorophenyl) acetamide, and 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[2-(hydroxymethyl-6-methylphenyl] acetamide.

This invention includes a subset of substituted piperazine compounds of formula I having the following formula IB:



IB

wherein m = 0, 1 or 2 or 3;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22};

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen or $C_{1\text{-}15}$ alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, CO_2R_{23}, $CON(R_{23})_2$, $C_{1\text{-}4}$ alkyl, or aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ or aryl, wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl wherein R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a bridging ring system wherein the two R groups together comprise of from 1 to 4 carbon atoms and wherein R^9 and R^{10} or R^{11} and R^{12} or R^{13} and R^{14} or R^{15} and R^{16} may join to form a spiro ring system wherein the two R groups together comprise of from 1 to 5 carbon atoms;

R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22} or wherein R^{17} and R^{18} may join together may join together to form –CH=CH-CH=CH- or wherein R^{17} and R^{18} or R^{18} and R^{19} or R^{19} and R^{20} or R^{20} and R^{21} may combine to form a saturated ring including from 3 to 6 carbon atoms wherein from 0 to 2 carbon atoms may be substituted with an oxygen atom and wherein the ring may be optionally substituted with from 1 to 3 substituents selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR^{23}, SR^{23}, $N(R^{23})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{23})_2$, $NR^{23}CO_2R^{22}$, $NR^{23}CON(R^{23})_2$, COR^{23}, CO_2R^{23}, $CON(R^{23})_2$, $NR^{23}SO_2R^{23}$, $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR^{23}, SR^{23}, $N(R^{23})_2$, $S(O)R^{22}$, or SO_2R^{22};

R_{22} is selected from the group consisting of C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, or heteroaryl; and

R_{23} is selected from the group consisting of H, C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, mono- or dialkylamino, alkyl, CN, -O-C_{1-6} alkyl, or CF_3.

In preferred compositions of this invention, m = 0, 1 or 2 or 3; R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR_{22} and C_{1-4} alkyl; R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and C_{1-3} alkyl; R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl, or R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl, or wherein R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a ring including from 1 to 4 carbon atoms wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are not all hydrogen; and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR^{22}, $S(O)R^{22}$, SO_2R^{22}, $SON(R^{22})_2$, $CON(R^{22})_2$, C_{1-4} alkyl or R^{17} and R^{18} may together form -CH=CH-CH=CH-, and phenyl.

In other preferred compounds, R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-2} alkyl wherein R_{22} is a C_{1-3} alkyl; R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen and methyl; R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen and C_{1-2} alkyl, or R^9 and R^{10} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl with the proviso that R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are not all simultaneously hydrogen and wherein R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join to form a ring including from 1 to 4 carbon atoms and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR^{22}, and C_{1-4} alkyl wherein R^{22} is C_{1-3} alkyl, and wherein R^{17} and R^{18} may together form a substituent selected from the group consisting of -CH=CH-CH=CH- and phenyl.

In still other preferred compounds, m = 1 or 2; R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-4} alkyl where R^{22} is a C_{1-3} alkyl; R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each

independently selected from hydrogen and methyl; R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22}, C_{1-3} alkyl where R^{22} is methyl, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$.

In more preferred compounds, m = 1 or 2;; R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each independently selected from methyl and hydrogen; R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each hydrogen; and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} wherein R^{22} is methyl, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$.

In yet other preferred compounds, m = 1 or 2;; R^1 and R^5 are methyl; R^2, R^3, R^4 R^6, R^7, R^8,R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are hydrogen; R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, OR^{22} wherein R^{22} is methyl, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$.

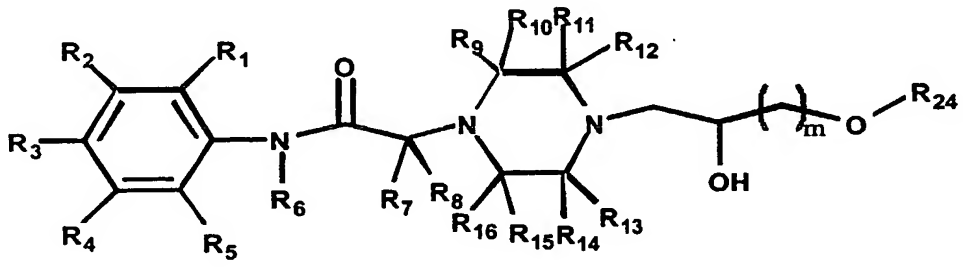
In still other preferred compounds, R^1 and R^5 are methyl; R^2, R^3, R^4, R^6, R^7, R^8,R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are hydrogen; R^{17} is selected from the group consisting of hydrogen, chloro, fluoro and methoxy; R^{18} is selected from hydrogen and methoxy; R^{19} is selected from hydrogen and methoxy; R^{20} is hydrogen; R^{21} is selected from hydrogen and chloro, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$.

Most preferably, the substituted piperazine compounds of this invention are selected from N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-4-phenylbutyl)piperazinyl]acetamide; N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenyl)propyl]piperazinyl}acetamide; 2-[4-(3-(2H-benzo[d]1,3-dioxolen-5-yl)-2-hydroxypropyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide; N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(4-methoxyphenyl)propyl]piperazinyl}acetamide; N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-phenylpropyl]piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[4-(4-methoxyphenyl)-2-hydroxybutyl]piperazinyl}acetamide, 2-{4-[4-(2,6-difluorophenyl)-2-hydroxybutyl]piperazinyl}-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-{4-[4-(2-chlorophenyl)-2-hydroxybutyl]piperazinyl}acetamide, 2-(4-{4-[4-(tert-butyl)phenyl]-2-hydroxybutyl}piperazinyl)-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-{4-[4-(2-fluorophenyl)-2-hydroxybutyl]piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-4-[4-(trifluoromethyl)phenyl]butyl}piperazinyl)acetamide, 2-[4-(3-(2H-benzo[d]1,3-dioxolen-5-yl)-2-hydroxypropyl)piperazinyl]-N-(2,6-dimethylphenyl)-2-methylpropanamide,

N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-phenylpropyl)piperazinyl]-2-methylpropanamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(3,4,5-trimethoxyphenyl)propyl]piperazinyl}-2-methylpropanamide,

N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-5-phenylpentyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-{4-[5-(2-fluorophenyl)- 2-hydroxy-pentyl]piperazinyl}acetamide, and N-(2,6-dimethylphenyl)-2-{4-[5-(2-chlorophenyl)- 2-hydroxy-pentyl]piperazinyl}acetamide.

This invention further includes a subset of compounds of Formula I above having the following Formula IC:



IC

wherein m = 1, 2, or 3;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}SO_2R^{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, and SO_2R^{22} ;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen or C_{1-3} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, CO_2R^{20}, $CON(R^{20})_2$, C_{1-4} alkyl, or aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR^{20}, $N(R^{20})_2$, CO_2R^{20}, $CON(R^{20})_2$ or aryl, wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl with the proviso that R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a ring including from 1 to 3 carbon atoms;

R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl,

cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to three substituents selected from the group consisting of halo, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, C_{1-2} alkyl, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl;

R^{20} is selected from the group consisting of H, C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, mono- or dialkylamino, alkyl, CN, -O-C_{1-6} alkyl, or CF_3; and

R^{22} is selected from the group consisting of C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, or heteroaryl.

In Formula IC, it is preferred that m = 1 or 2 and most preferred when m = 1.

In preferred compositions of Formula IC, R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-4} alkyl and wherein R^{22} is a C_{1-3} alkyl. In other preferred compositions, R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, CF_3, OR^{20}, or C_{1-2} alkyl. More preferably R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, or methyl with R^2, R^3, and R^4 as hydrogen and R^1 and R^5 as methyl being preferred.

In other preferred compositions of Formula IC, R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and C_{1-3} alkyl with hydrogen or methyl being preferred and hydrogen being most preferred.

In yet other preferred compositions of Formula IC, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, $CON(R^{20})_2$, C_{1-4} alkyl, or aryl wherein the alkyl and aryl substituents are each optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, OR^{20}, $N(R^{20})_2$, $CON(R^{20})_2$ or aryl wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl with the proviso that R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a ring. In alternative preferred compositions, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl, or R^9 and R^{10} together form a carbonyl, or R^{11} and R^{12} together form a carbonyl, or R^{13} and R^{14} together form a carbonyl, or R^{15} and R^{16} together form a carbonyl, R^{10} and R^{11} together form $-CH_2CH_2CH_2CH_2-$. In another embodiment, R^9, R^{10}, R^{11}, R^{12}, R^{13},

R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, or C_{1-2} alkyl, wherein the alkyl substituent is optionally substituted with 1 substituent selected from the group consisting of $N(R^{20})_2$, or aryl or wherein R^9 and R^{10} may together form a carbonyl. More preferably, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen or C_{1-2} alkyl, or wherein R^9 and R^{10} may together form a carbonyl. In another embodiment, R^{11} and R^{15} are each selected from the group consisting of hydrogen or methyl, R^9, R^{10}, R^{12}, R^{13}, R^{14} and R^{16} are each hydrogen and R^9 and R^{10} may together form a carbonyl, or, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} may each be hydrogen.

In compounds of Formula IC, R_{24} may be selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to three substituents selected from the group consisting of halo, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, C_{1-2} alkyl, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl. In certain preferred compounds of Formula IC, R_{24} is selected from the group consisting of alkyl , cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to two substituents selected from the group consisting of halo, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, C_{1-2} alkyl, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl. In other preferred compounds of Formula IC, R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to two substituents selected from the group consisting of halo, CF_3, OR^{20}, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl. In still other preferred compounds of Formula IC, R_{24} is selected from the group consisting of alkyl having from 1 to 6 carbon atoms, cycloalkyl having from 4 to 6 carbon atoms, fused phenylcycloalkylwith a phenyl that is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, CF_3, OH, methyl, and aryl, and aryl that is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, CF_3, OH, C_{1-2} alkyl, and aryl. In still other preferred compounds of Formula IC, R_{24} is alkyl having from 1 to 6 carbon atoms and cycloalkyl or R_{24} is a fused phenylcycloalkyl that is

optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, CF_3, OR^{20}, C_{1-2} alkyl, and aryl or R_{24} is phenylmethyl that is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, CF_3, OR^{20}, C_{1-4} alkyl, and aryl.

In the compounds of Formula IC, R^{20} is selected from the group consisting of H, C_{1-3} alkyl, or aryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent individually selected from the group consisting of halo, -OMe, and CF_3. More preferably, R^{20} is selected from the group consisting of H or C_{1-3} alkyl and most preferably, R^{20} is methyl or H.

Most preferably, the substituted piperazine compounds of Formula IC are selected from the group consisting of 2-({2-[4-(3-isopropoxy-2-hydroxypropyl)piperazinyl]- N-({2,6-dimethylphenyl)acetamide; N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indan-2-yloxypropyl)piperazinyl]acetamide; N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(phenylmethoxy)propyl]piperazinyl}acetamide, 2-[4-(3-{[4-(tert-butyl)phenyl]methoxy}-2-hydroxypropyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{3-[(2-fluorophenyl)methoxy]-2-hydroxypropyl}piperazinyl)acetamide, 2-(4-{3-[(2,4-difluorophenyl)methoxy]-2-hydroxypropyl}piperazinyl)-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-{[4-(trifluoromethyl)phenyl]methoxy}propyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(2-methoxyphenyl)methoxy]propyl}piperazinyl)acetamide, 2-(4-{3-[(2,4-dimethoxyphenyl)methoxy]-2-hydroxypropyl}piperazinyl)-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(4-methoxyphenyl)methoxy]propyl}piperazinyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{3-[(4-fluorophenyl)methoxy]-2-hydroxypropyl}piperazinyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(4-methylphenyl)methoxy]propyl}piperazinyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(4-phenylphenyl)methoxy]propyl}piperazinyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{3-[(4-butylphenyl)methoxy]-2-hydroxypropyl}piperazinyl)acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydoxy-3-(2-naphthylmethoxy)propyl]piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[3-(cyclohexylmethoxy)-2-hydroxypropyl]piperazinyl}acetamide, and N-(2,6-dimethylphenyl)-2-(4-{3-[(4-fluorophenyl)methoxy]-2-hydroxypropyl}-3,3-dimethylpiperazinyl)acetamide.

The following definitions apply to terms as used herein.

"Halo" or "Halogen" - alone or in combination means all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), iodo (I).

"Hydroxyl" refers to the group -OH.

"Thiol" or "mercapto" refers to the group -SH.

"Alkyl" - alone or in combination means an alkane-derived radical containing from 1 to 20, preferably 1 to 15, carbon atoms (unless specifically defined). It is a straight chain alkyl, branched alkyl or cycloalkyl. Preferably, straight or branched alkyl groups containing from 1-15, more preferably 1 to 8, even more preferably 1-6, yet more preferably 1-4 and most preferably 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like. The term "lower alkyl" is used herein to describe the straight chain alkyl groups described immediately above. Preferably, cycloalkyl groups are monocyclic, bicyclic or tricyclic ring systems of 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl and the like. Alkyl also includes a straight chain or branched alkyl group that contains or is interrupted by a cycloalkyl portion. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. Examples of this include, but are not limited to, 4-(isopropyl)-cyclohexylethyl or 2-methyl-cyclopropylpentyl. A substituted alkyl is a straight chain alkyl, branched alkyl, or cycloalkyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Alkenyl" - alone or in combination means a straight, branched, or cyclic hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most preferably 2 to 4 carbon atoms with at least one, preferably 1-3, more preferably 1-2, and most preferably one, carbon to carbon double bond. In the case of a cycloalkyl group, conjugation of more than one carbon to carbon double bond is not such as to confer aromaticity to the ring. Carbon to carbon double bonds may be either contained within a cycloalkyl portion, with the exception of cyclopropyl, or within a straight chain or branched portion. Examples of alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, cyclohexenyl, cyclohexenylalkyl and the like. A substituted alkenyl is the straight chain alkenyl, branched alkenyl or cycloalkenyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea

optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, or the like attached at any available point to produce a stable compound.

"Alkynyl" - alone or in combination means a straight or branched hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most preferably 2-4, carbon atoms containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl and the like. A substituted alkynyl refers to the straight chain alkynyl or branched alkynyl defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like attached at any available point to produce a stable compound.

"Alkyl alkenyl" refers to a group -R-CR'=CR''' R'''', where R is lower alkyl, or substituted lower alkyl, R', R''', R'''' may independently be hydrogen, halogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkyl alkynyl" refers to a groups -RC≡CR' where R is lower alkyl or substituted lower alkyl, R' is hydrogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkoxy" denotes the group -OR, where R is lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroalkyl, heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl as defined.

"Alkylthio" denotes the group -SR, $-S(O)_{n=1-2}-R$, where R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl as defined herein.

"Acyl" denotes groups -C(O)R, where R is hydrogen, lower alkyl substituted lower alkyl, aryl, substituted aryl and the like as defined herein.

"Aryloxy" denotes groups -OAr, where Ar is an aryl, substituted aryl, heteroaryl, or substituted heteroaryl group as defined herein.

"Amino" denotes the group NRR', where R and R' may independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined herein or acyl.

"Amido" denotes the group -C(O)NRR', where R and R' may independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, substituted hetaryl as defined herein.

"Carboxyl" denotes the group -C(O)OR, where R is hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, and substituted hetaryl as defined herein.

"Aryl" - alone or in combination means phenyl or naphthyl optionally carbocyclic fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members and/or optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Substituted aryl" refers to aryl optionally substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring (*e.g.*, morpholino, pyridyl or furyl) or multiple condensed rings (*e.g.*, naphthpyridyl, quinoxalyl, quinolinyl, indolizinyl or benzo[b]thienyl) and having at least one hetero atom, such as N, O or S, within the ring, which can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroaryl" - alone or in combination means a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group O, S, and N, and optionally substituted with 1 to 3

groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable aromatic ring is retained. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrazinyl, quinazolinyl, purinyl, quinolinyl, isoquinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, indolyl, benzothiazolyl, benzoxazolyl, and the like. A substituted heteroaryl contains a substituent attached at an available carbon or nitrogen to produce a stable compound.

"Heterocyclyl" - alone or in combination means a non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally benzo fused or fused heteroaryl of 5-6 ring members and/or are optionally substituted as in the case of cycloalkyl. Heterocycyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment is at a carbon or nitrogen atom. Examples of heterocyclyl groups are tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl, dihydrobenzofuryl, dihydroindolyl, and the like. A substituted hetercyclyl contains a substituent nitrogen attached at an available carbon or nitrogen to produce a stable compound.

"Substituted heteroaryl" refers to a heterocycle optionally mono or poly substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Aralkyl" refers to the group -R-Ar where Ar is an aryl group and R is lower alkyl or substituted lower alkyl group. Aryl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroarylalkyl" refers to the group -R-HetAr where HetAr is an heteroaryl group and R lower alkyl or substituted lower alkyl. Heteroarylalkyl groups can optionally be

unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Cycloalkyl" refers to a divalent cyclic or polycyclic alkyl group containing 3 to 15 carbon atoms.

"Substituted cycloalkyl" refers to a cycloalkyl group comprising one or more substituents with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Alkyl cycloalkyl" denotes the group -R-cycloalkyl where cycloalkyl is a cycloalkyl group and R is a lower alkyl or substituted lower alkyl. Cycloalkyl groups can optionally be unsubstituted or substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Optional" and "optionally" mean that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optional pharmaceutical excipients" indicates that a formulation so described may or may not include pharmaceutical excipients other than those specifically stated to be present, and that the formulation so described includes instances in which the optional excipients are present and instances in which they are not.

"Treating" and "treatment" refer to any treatment of a disease in a mammal, particularly a human, and include:

(i) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it;

(ii) inhibiting the disease, i.e., arresting its development; or

(iii) relieving the disease, i.e., causing regression of the disease.

The compositions of this invention are useful for treating mammals in a therapy selected from the group consisting of protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, and to treat cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction. The treatment is accomplished using a therapeutically

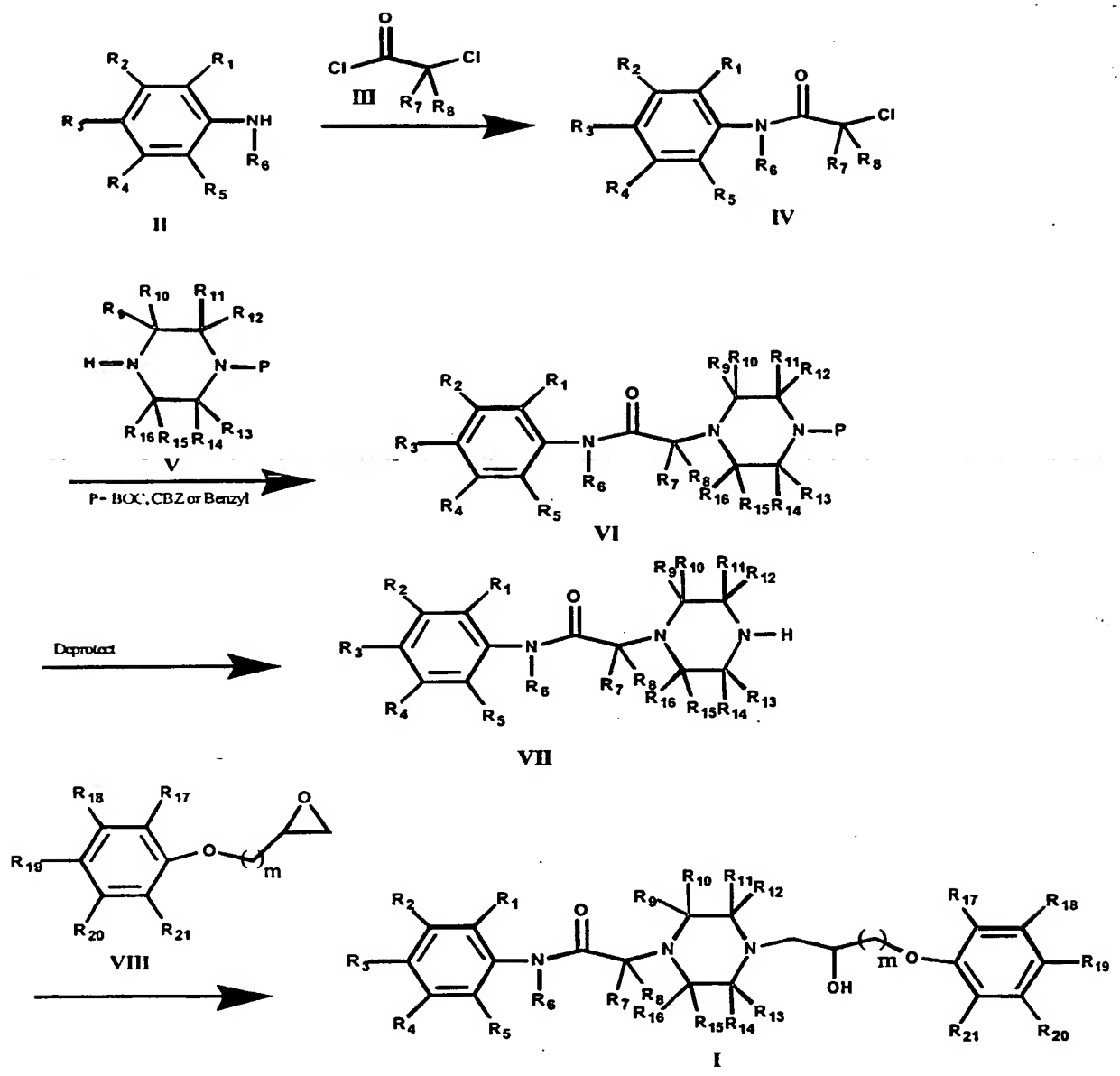
effective amount of at least one compound of this invention and/or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutically acceptable excipient.

Compounds falling within the scope of this invention include the optical isomers (+) and (-) and R- and S- isomers of the above-identified compounds and mixtures thereof. This invention includes the individual isomers and all possible mixtures thereof.

All of the aforementioned embodiments include the pharmaceutically acceptable acid addition salts thereof, particularly the mono- and dihydrochlorides, and mixtures thereof.

The compounds having the general Formula I and IA can be prepared as outlined in Schemes 1A-7A. A general synthesis of the compounds of this invention is outlined in Scheme 1A. Compound IV can be prepared by N-acylation of substituted aniline II with 2-substituted chloroacetylchloride III. Compound II is available commercially or readily prepared through reduction of the corresponding nitrobenzene derivative (acid/$SnCl_2$ or catalytic hydrogenation, see Advanced Organic Chemistry, Ed. J. March, (1992) A. Wiley-Interscience). Some examples of commercially available substituted anilines corresponding to general structure II include 2,6-dimethylaniline, 2,3-dimethylaniline, 2-methylaniline, 4-methylaniline, 4-methylaniline, 2,4-dichloroaniline, 3,4-dichloroaniline, 2,5-dichloroaniline, 2,4-dichloroaniline, 2-chloroaniline, 3-chloroaniline, 2,6-difluoroaniline, 2,5-difluoroaniline, 3,4-difluoroaniline, 2-fluoroaniline, 4-fluoroaniline, 3-fluoroaniline, 2-fluoro-6-chloroaniline, 4-fluoro-3-chloroaniline.

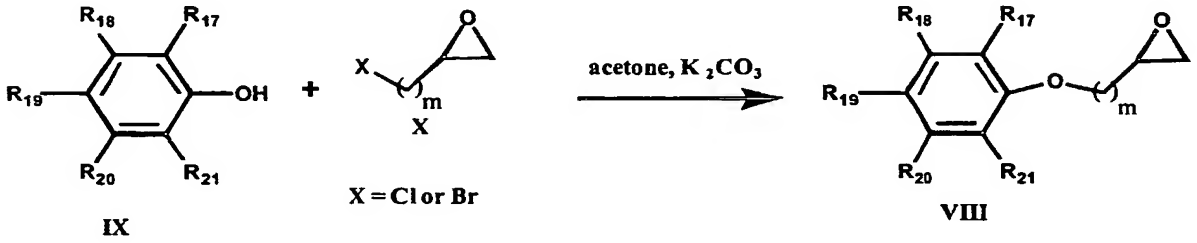
SCHEME 1



Compound VI can be obtained by reacting compound IV with N-protected substituted piperazine V through warming in an appropriate solvent (e.g. DMF, EtOH). Protection of the nitrogen of compound V is only required when it is useful to control the regiochemistry of the addition of Compound V with compound IV. In some cases, compound V can be obtained from commercial resources. Examples of commercially available compounds corresponding to general structure V include 2-methyl piperazine, 2,5-

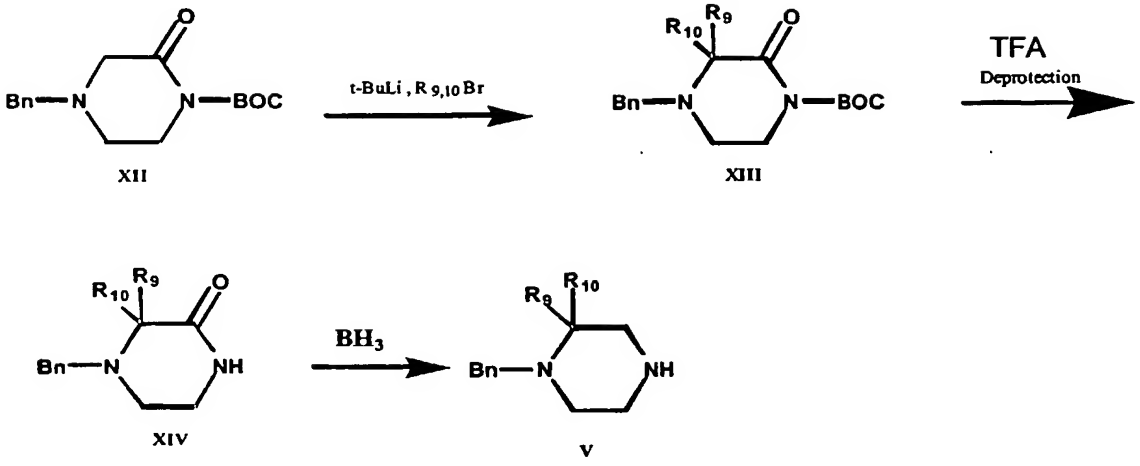
dimethyl piprazine and 2,6-dimethyl piperazine. Deprotection of compound VI can be accomplished using the standard conditions (e.g. for Boc group use TFA, for CBZ and benzyl use hydrogenation). Compound I can be prepared by reacting compound VII with epoxide VIII through warming in an appropriate solvent (ethanol, DMF).

SCHEME 2A



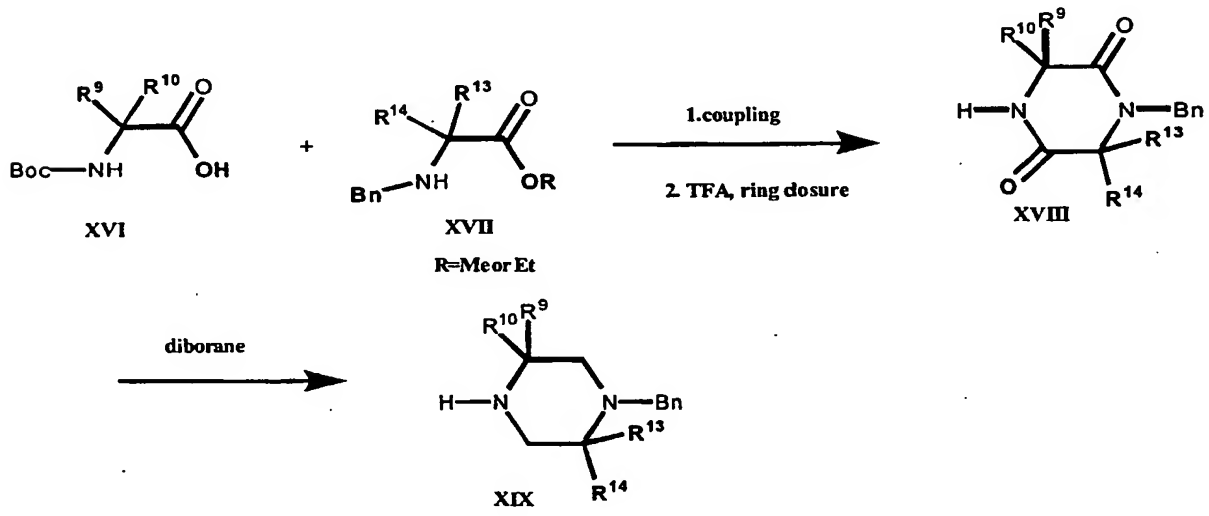
Epoxide VIII (where m = 1 or 2) can be prepared as outlined in Scheme 2. Heating substituted phenol IX with epichlorohydrin, epibromohydrin, or 4-bromo-1,2-epoxybutane and potassium carbonate in acetone can afford epoxide VIII. Compound IX can be obtained from commercial resources. Example of commercially available compounds of compounds XI include 2-chlorophenol, 2-fluorophenol, 2-methoxyphenol, 2-methylphenol, sesamol, 2,6-dichlorophenol, 3,5-dichlorophenol, 2,6-difluorophenol, 2,4-difluorophenol5-indanol, 3-chloro-4-fluorophenol, 2,chloro-4-fluorophenol and 5,6,7,8-tetrahydro-2-naphthol. In some cases compound VIII can be obtained from commercial sources. Examples of commercially available compounds corresponding to general structure VIII include benzyl glycidyl ether, glycidyl 2-methylphenyl ether, glycidyl 4-methoxyphenyl ether, glycidyl 4-chlorophenyl ether, glycidyl 2-chlorophenyl ether, glycidyl 2-methoxyphenyl ether, glycidyl 4-methylphenyl ether, glycidyl 3,4-dichlorophenyl ether and glycidyl 4-fluorophenyl ether.

SCHEME 3A



Compound V can be prepared as described in Scheme 3. Alkylation of compound XII with alkyl halides using t-BuLi as base can afford compound XIII as described by Pohlman et. al. (J. Org. Chem, (1997), 62, 1016-1022). Reduction of XIV using diborane can afford N-benzyl protected version of compound V after N-Boc deprotection with trifluoroacetic acid (TFA) [for the diborane reduction see Jacobson et. al, J. Med. Chem, (1999), 42, 1123-1144].

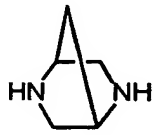
SCHEME 4A



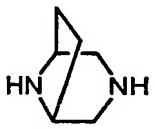
Compound V can also be prepared through standard coupling (eg. EDC or PyBroP) of D or L amino acids and standard deprotection as outlined in Scheme 4 [For preparations of diketopiperazines see – P. Cledera et al. Tetrahedron, (1998) p. 12349-12360 and R. A. Smith

et al Bioorg. Med. Chem. Lett. (1998) p. 2369-2374]. Reduction of the diketopiperazine with diborane can afford compound XIX the N-benzyl protected version of compound V.

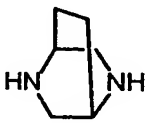
Compound V also includes the bicyclic homologs of piperazine (1S,4S)-(+)-2,5-diazabicyclo[2.2.1]heptane **83**, 3,8-diazabicyclo[3.2.1] octane **84**, and 2,5-diazabicyclo[2.2.2] octane **85**.



83



84

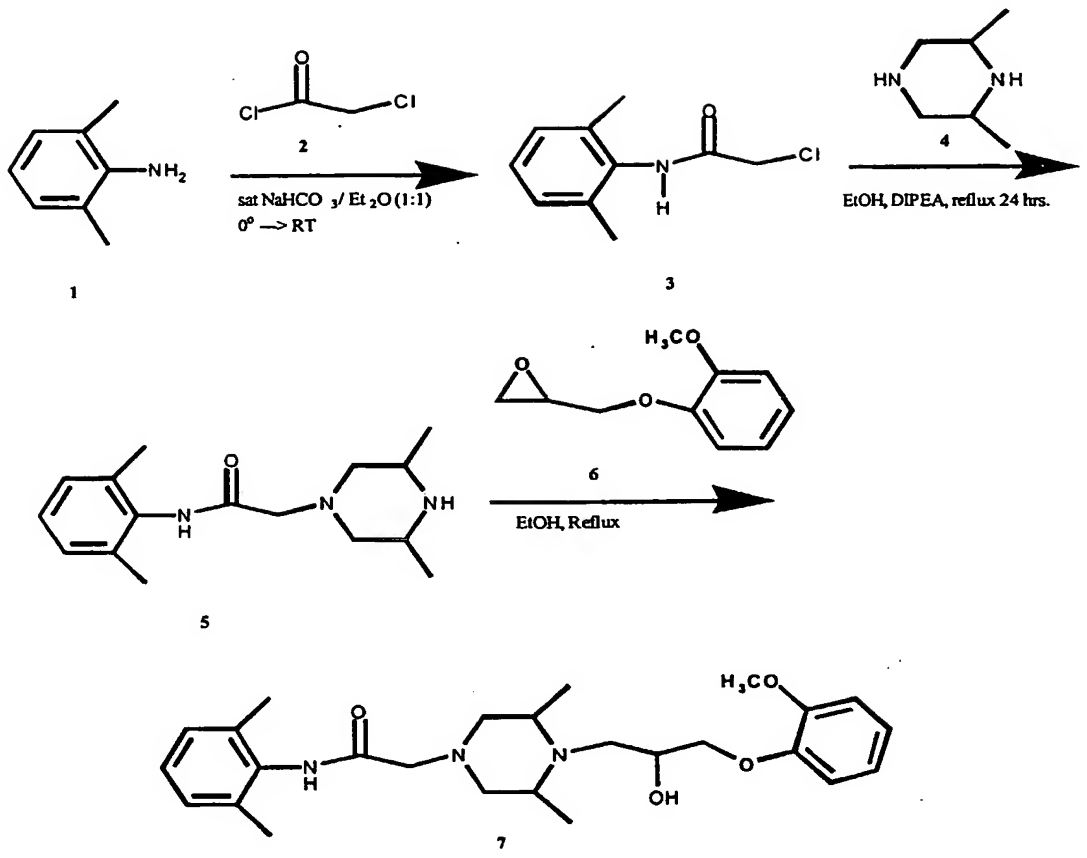


85

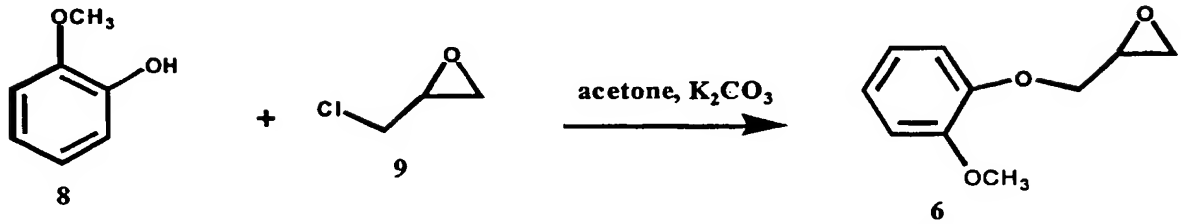
Commercially available bicyclic analogs include (1S,4S)-(+)-2,5-diazabicyclo[2.2.1]heptane **83**. Compounds **84**, **85**, and the (1R,4R) isomer of **83** can be prepared by published procedures (for **84** and **85**- see Sturm, P. A. *et al*, J. Med. Chem. **1974**, *17*, 481-487; for **83** see- Barish, T. F. and Fox, D. E. J. Org. Chem., **1990**, *55*, 1684-1687).

A specific example of the preparation of a compound of Formula IA is disclosed in Schemes 5A, 6A and 7A to further illustrate how to prepare the compounds of this invention. In particular, 2,6-dichloroaniline was acylated with 2-chloroacetyl chloride 2 using saturated bicarbonate and ether (1:1) as base and co-solvent, respectively to afford the chloroacetamide derivative 3. Further reaction of compound 3 with 2,6-dimethyl piperazine afforded compound 5 through warming in ethanol. Reaction of compound 5 with epoxide 6 by warming both components in ethanol at reflux afforded 2,6-dimethyl piperazine derivative 7. Compound 6 in turn was prepared by warming epichlorohydrin with 2-methoxyphenol in acetone in the presence of K_2CO_3 as described in Scheme 6.

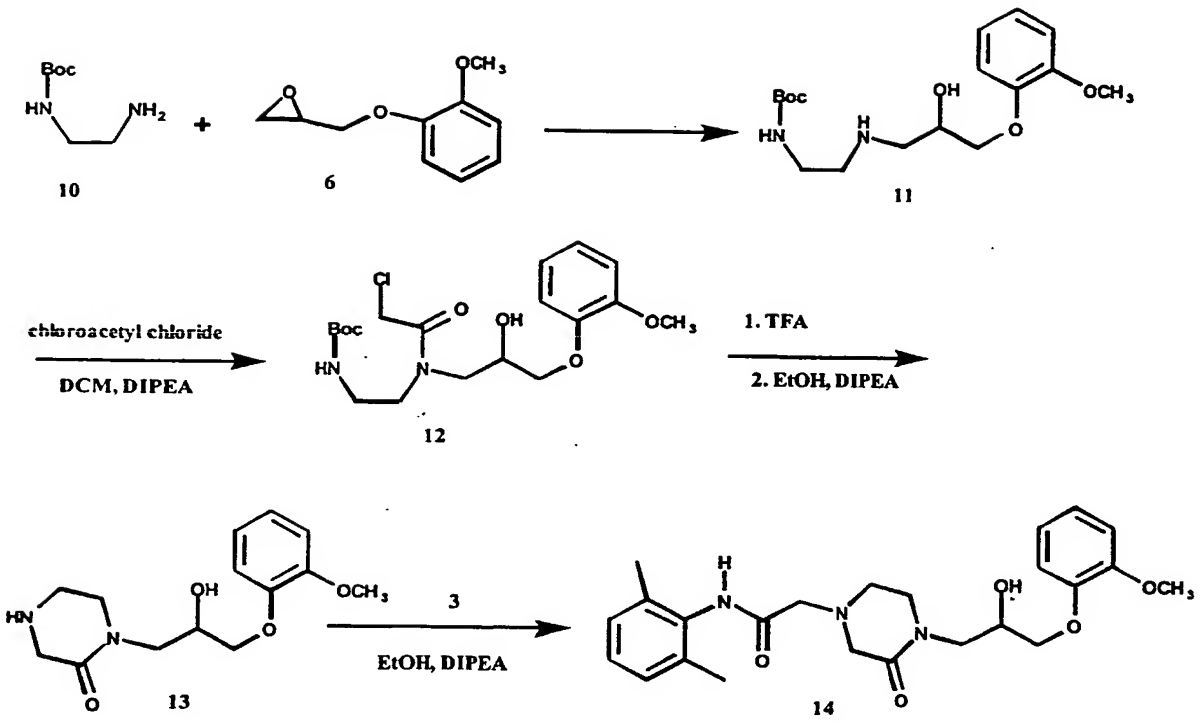
SCHEME 5A



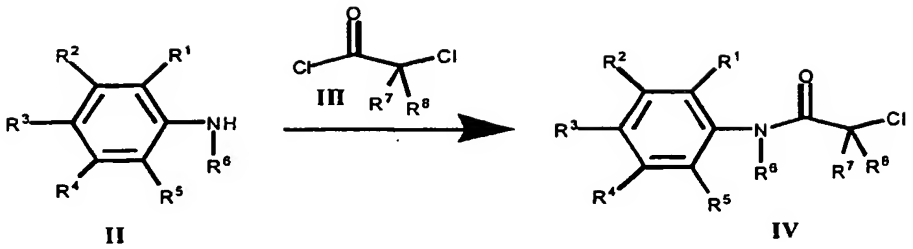
SCHEME 6A



A specific synthesis of compound 14 is described in Scheme 7. Compound 11 was prepared by opening of epoxide 6 with Boc-ethylenediamine through warming in EtOH. Acylation of compound 11 was accomplished using chloroacetyl chloride in dichloromethane using diisopropylethyl amine as a base. Removal of the Boc group using TFA followed by ring closure through warming in EtOH afforded compound 13. Reaction of compound 13 with 6 as described above afforded compound 14.



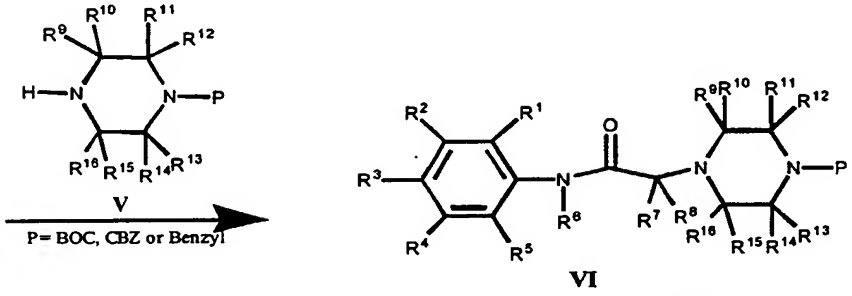
The compounds having the general formula **I** and IB can be prepared as outlined in Schemes 1B-7B. A general synthesis of the compounds of this invention is outlined in Scheme 1B. Compound **IV** can be prepared by N-acylation of substituted anilines of general structure **II** with 2-substituted chloroacetylchloride **III**. Compound **II** is available commercially or readily prepared through reduction of the corresponding nitrobenzene derivative (acid/$SnCl_2$ or catalytic hydrogenation, see Advanced Organic Chemistry, Ed. J. March, (1992) A. Wiley-Interscience). Some examples of commercially available substituted anilines of general structure **II** include 2,6-dimethylaniline, 2,3-dimethylaniline, 2-methylaniline, 4-methylaniline, 2,4-dichloroaniline, 3,4-dichloroaniline, 2,5-dichloroaniline, 2,4-dichloroaniline,. 2-chloroaniline, 3-chloroaniline, 2,6-difluoroaniline, 2,5-difluoroaniline, 3,4-difluoroaniline, 2-fluoroaniline, 4-fluoroaniline, 3-fluoroaniline, 2-fluoro-6-chloroaniline, 4-fluoro-3-chloroaniline.



II

III

IV

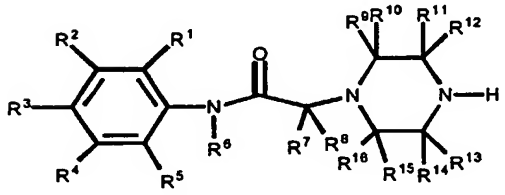


V

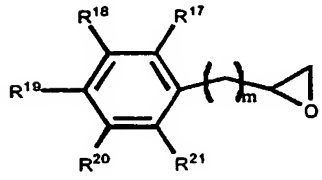
P= BOC, CBZ or Benzyl

VI

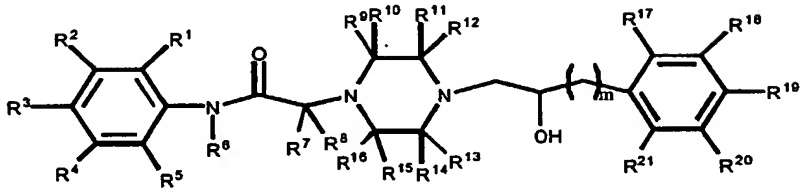
Deprotect



VII



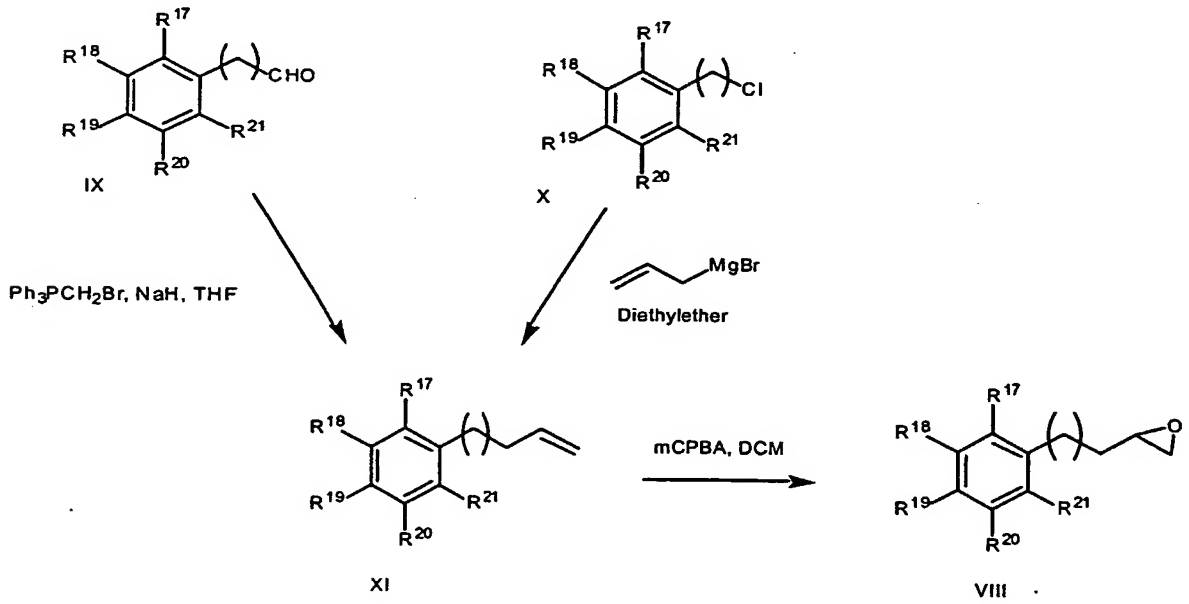
VIII



I

Compound **VI** can be obtained by reacting compound **IV** with a N-protected substituted piperazine **V** through warming in an appropriate solvent (e.g. DMF, EtOH). Protection of the nitrogen of compound **V** is only required when it is useful to control the regiochemistry of the addition of Compound **V** with compound **IV**. In some cases, compound **V** can be obtained from commercial sources. Examples of commercially available compounds of general structure **V** include 2-methyl piperazine, 2,5-dimethyl piperazine and 2,6-dimethyl piperazine. Deprotection of compound **VI** can be accomplished using the standard conditions (e.g. for Boc group use TFA, for CBZ and benzyl use hydrogenation). Compound **I** can be prepared by reacting compound **VII** with epoxide **VIII** through warming in an appropriate solvent (ethanol, DMF).

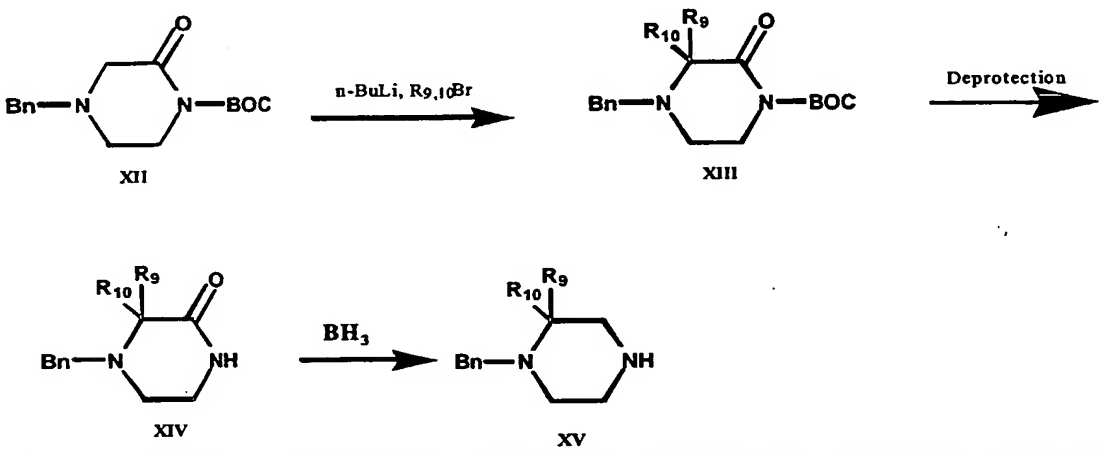
SCHEME 2B



Epoxide **VIII** can be prepared as outlined in Scheme 2B. Epoxidation of substituted allylbenzene **XI** using mCPBA or hydrogen peroxide can afford epoxide **VIII** (G. Majetich, R. Hicks, G. Sun and P. McGill, (1998), 63, 2564-2573). Compound **XI** in turn can be prepared by reacting aldehyde **IX** with methylenetriphenylphosphorane under Wittig conditions or Horner Emmons conditions [Advanced Organic Chemistry, Eds. J. March,

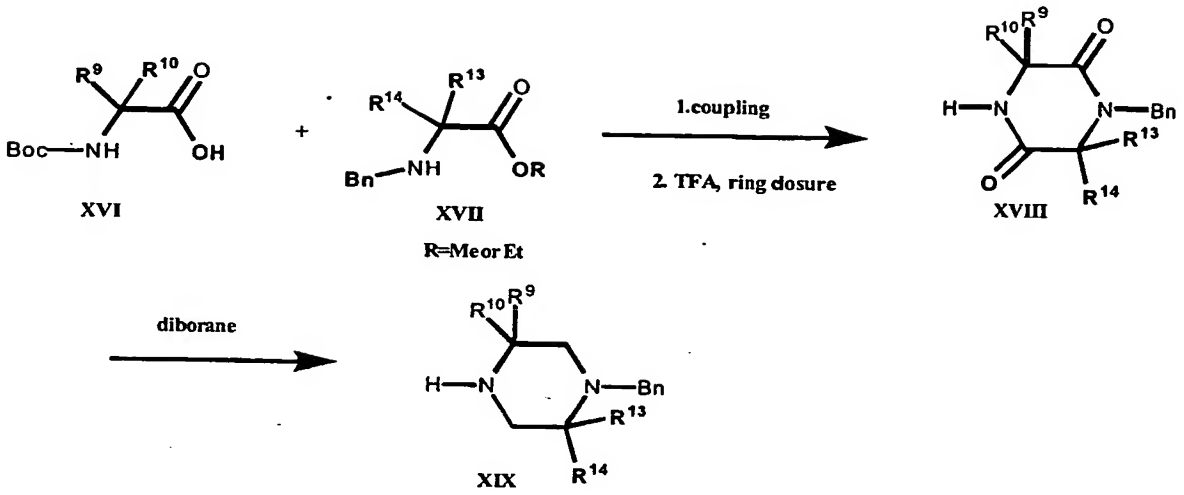
(1992), Wiley-Interscience publication and S. Pine, G. Shen and H. Hoang, Synthesis, (1991), 1]. The compound XI can also be conveniently prepared by coupling a halide with the general formula X with allyl magnesium bromide. In some cases compound **XI** can be obtained from commercial sources. Examples of commercially available compounds corresponding to the general structure **XI** include (where m = 0) 3-fluorostyrene, 4-fluorostyrene, 2-chlorostyrene, 3-chlorostyrene, 4-chlorostyrene, 2,6-dichlorostyrene, 3,4-dichlorostyreneand 3,4-dimethoxystyrene. Other examples of commercially available compounds with the general structure **XI** include (where m = 1) 4-methoxyallylbenzene, 2-hydroxyallylbenzene, 4,5-dimethoxyallylbenzene, 2-methylallylbenzene safrole and 1-allylnaphthalene.

SCHEME 3B



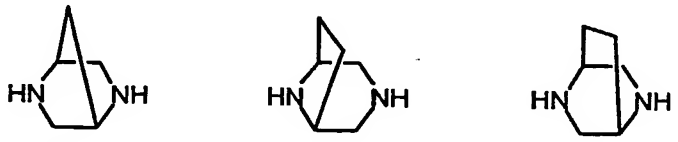
Compound V can be prepared as described in Scheme 3B. Alkylation of compound **XII** with alkyl halides using t-BuLi as base can afford compound **XIII** as described by Pohlman et. al. (J. Org. Chem, (1997), 62, 1016-1022). Reduction of **XIII** using diborane can afford N-benzyl protected version of compound **V** after N-Boc deprotection with trifluoroacetic acid (TFA , for the diborane reduction see Jacobson et. al, J. Med. Chem, (1999), 42, 1123-1144).

SCHEME 4B



Compound V can also be prepared through standard coupling (eg. EDC or PyBroP) of D or L amino acids and standard deprotection (e.g., Boc removal by TFA treatment) as outlined in Scheme 4 [For preparations of diketopiperazines see – P. Cledera et al. Tetrahedron, (1998) p. 12349-12360 and R. A. Smith et al Bioorg. Med. Chem. Lett. (1998) p. 2369-2374]. Reduction of the diketopiperazine with diborane can afford the N-benzyl protected version of compound V.

Compound V also includes the bicyclic homologs of piperazine (1S,4S)-(+)-2,5-diazabicyclo[2.2.1]heptane **83**, 3,8-diazabicyclo[3.2.1] octane **84**, and 2,5-diazabicyclo[2.2.2] octane **85**.



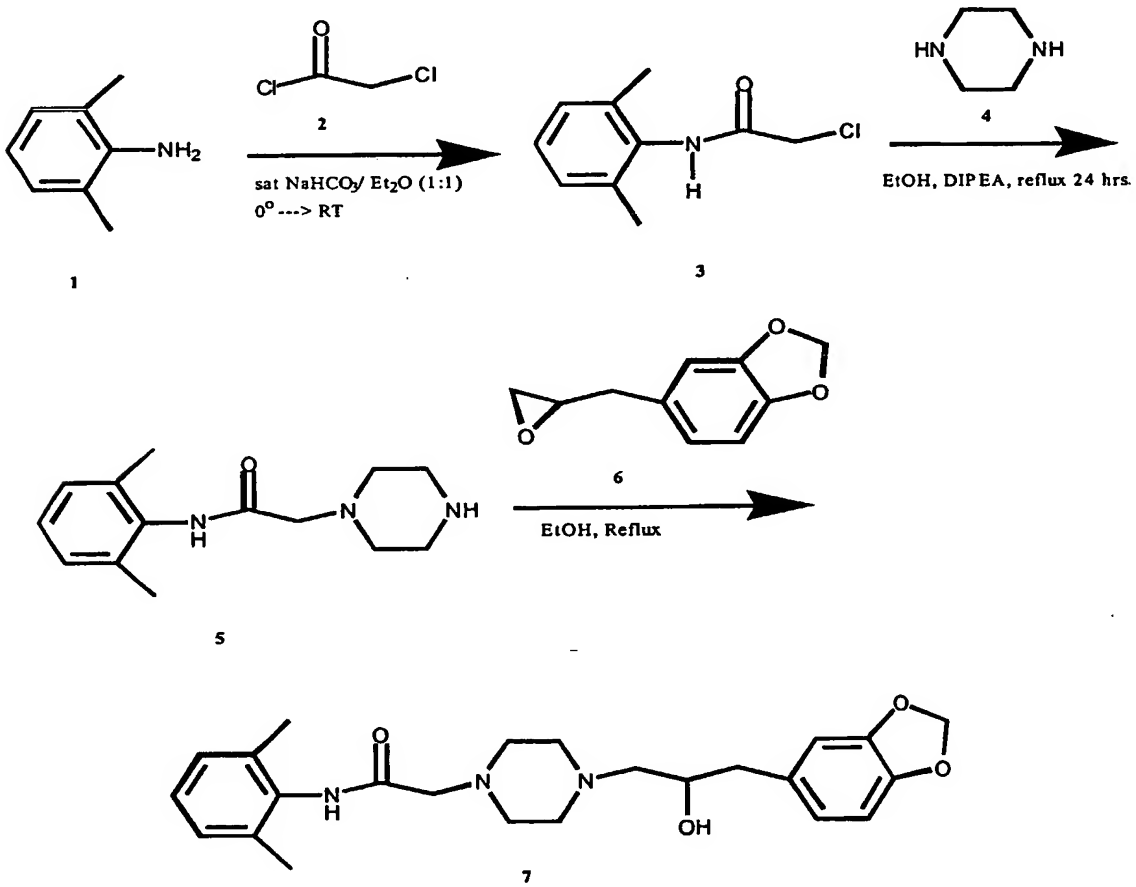
83 **84** **85**

Commercially available bicyclic analogs include (1S,4S)-(+)-2,5-diazabicyclo[2.2.1]heptane **83**. Compounds **84**, **85**, and the (1R,4R) isomer of **83** can be prepared by published procedures (for **84** and **85**- see Sturm, P. A. *et al*, J. Med. Chem. **1974**, *17*, 481-487; for **83** see- Barish, T. F. and Fox, D. E. J. Org. Chem., **1990**, *55*, 1684-1687).

A specific example of the preparation of a compound from this invention is disclosed in Scheme 5B to further illustrate how to prepare the compounds of this invention. In

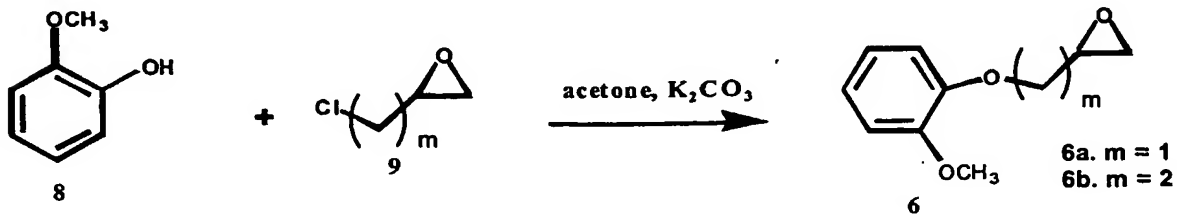
particular, 2,6-dichloroaniline was acylated with 2-chloroacetyl chloride **2** using saturated bicarbonate and ether (1:1) as base and co-solvent, respectively to afford the chloroacetamide derivative **3**. Further reaction of compound **3** with piperazine afforded compound **5** through warming in ethanol. Reaction of compound **5** with epoxide **6** by warming both components in ethanol at reflux afforded piperazine derivative **7**.

SCHEME 5B



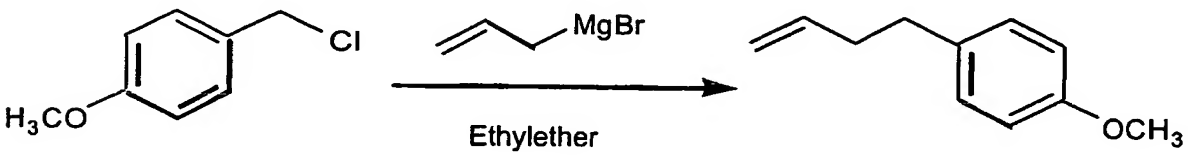
Compound **8** is commercially available and was epoxidized using 3-chloroperoxybenzioc acid in dichloromethane as illustrated in Scheme **6B**.

Scheme 6B

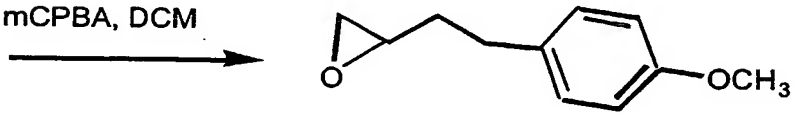


Four carbon epoxide 15 can be prepared by coupling commercially available 4-methoxybenzyl chloride with allylmagnesium bromide followed by oxidation with mCPBA as illustrated in Scheme 7B.

SCHEME 7B

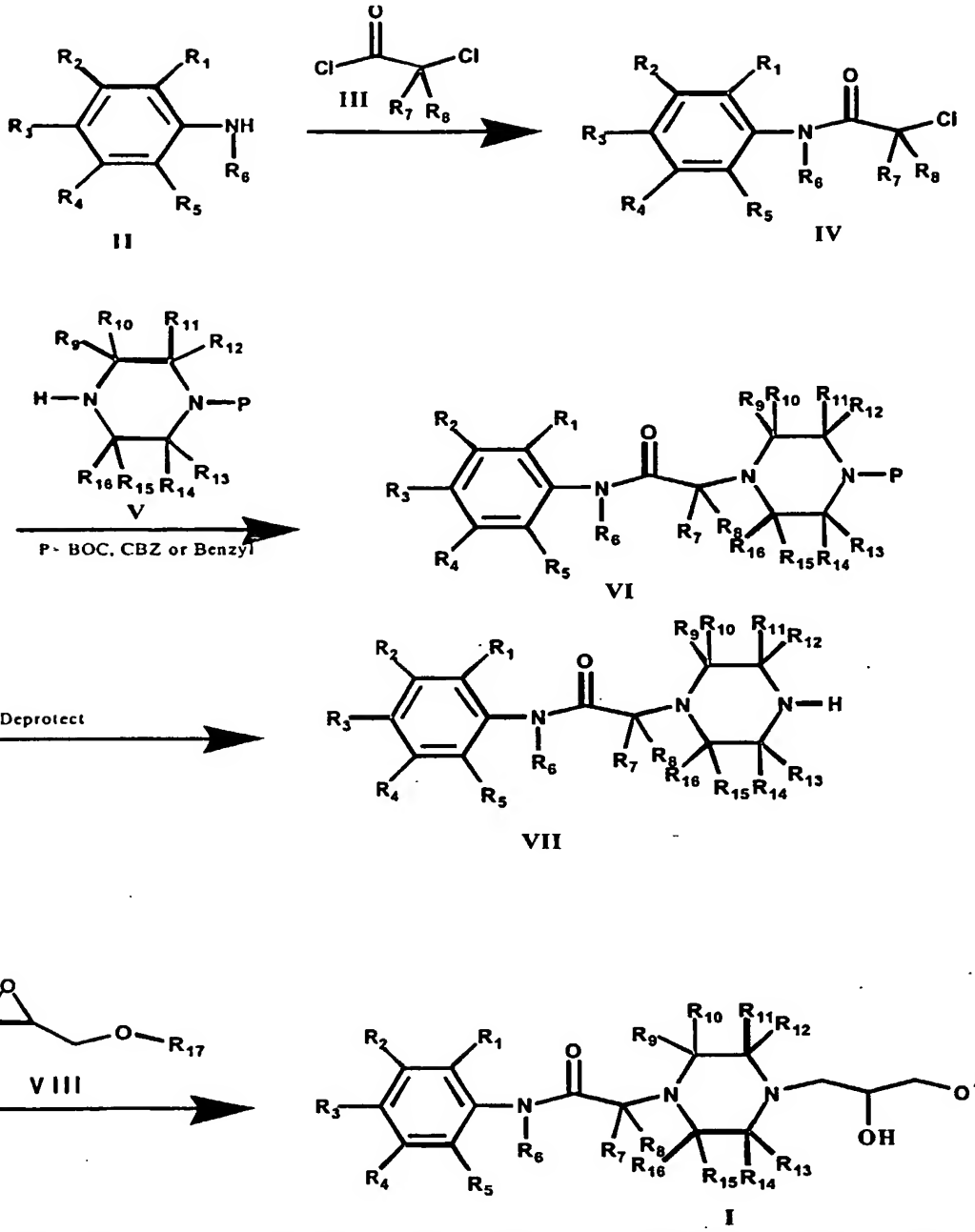


14



15

The compounds having the general Formula I and IC can be prepared as outlined in Schemes 1C-6C. A general synthesis of the compounds of this invention is outlined in Scheme 1C.

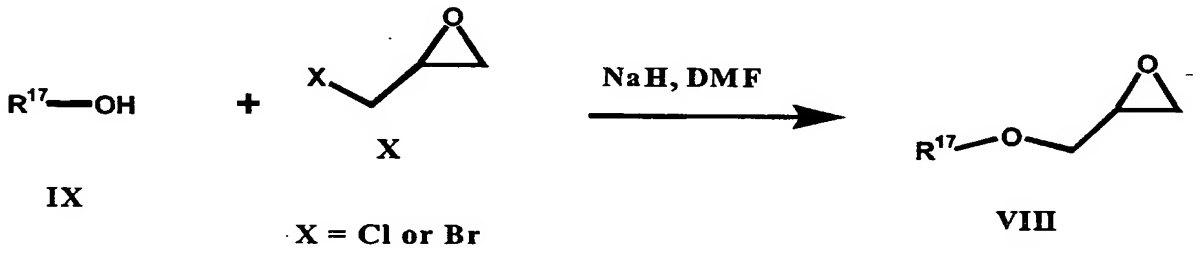


Compound **IV** can be prepared by N-acylation of substituted aniline **II** with 2-substituted chloroacetylchloride **III**. Compound **II** is available commercially or readily prepared through reduction of the corresponding nitrobenzene derivative (acid/$SnCl_2$ or catalytic hydrogenation, see Advanced Organic Chemistry, Ed. J. March, (1992) A. Wiley-Interscience). Some examples of commercially available substituted aniline **II** include 2,6-dimethylaniline, 2,3-dimethylaniline, 2-methylaniline 4-methylaniline, 4-methylaniline, 2,4-dichloroaniline, 3,4-dichloroaniline, 2,5-dichloroaniline, 2,4-dichloroaniline, 2-chloroaniline, 3-chloroaniline, 2,6-

difluoroaniline, 2,5-difluoroaniline, 3,4-difluoroaniline, 2-fluoroaniline, 4-fluoroaniline, 3-fluoroaniline, 2-fluoro-6-chloroaniline, 4-fluoro-3-chloroaniline.

Compound **VI** can be obtained by reacting compound **IV** with N-protected substituted piperazine **V** through warming in an appropriate solvent (e.g. DMF, EtOH). Protection of the nitrogen of compound **V** is only required when it is useful to control the regiochemistry of the addition of Compound **V** with compound **IV**. In some cases, compound **V** can be obtained from commercial sources. Examples of commercially available compound corresponding to the general structure **V** include 2-methyl piperazine, 2,5-dimethyl piperazine, 2,6-dimethyl piperazine and 4-benzyloxycarbonylpiperazin-2-one. Deprotection of compound **VI** can be accomplished using the standard conditions (e.g. for Boc group use TFA, for CBZ and benzyl use hydrogenation). Compound **I** can be prepared by reacting compound **VII** with epoxide **VIII** through warming in an appropriate solvent (ethanol, DMF).

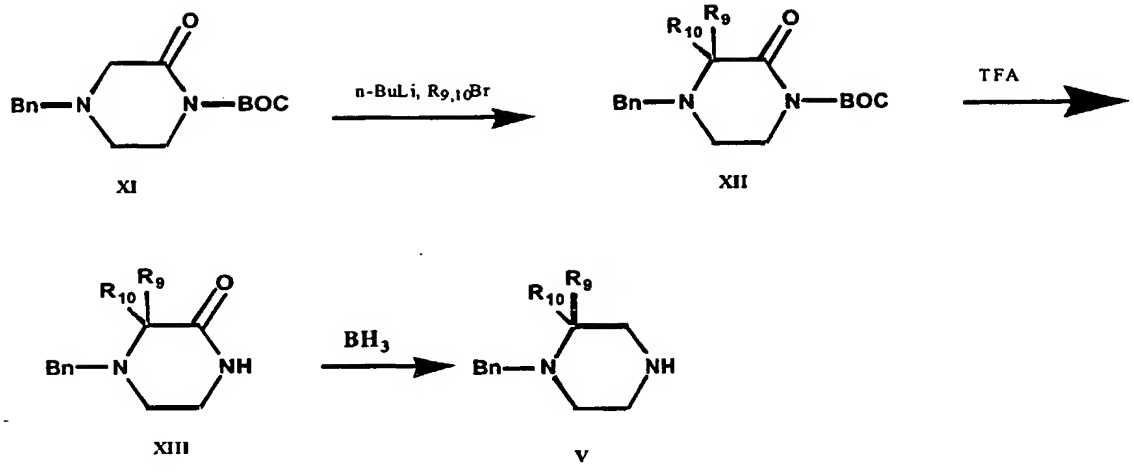
SCHEME 2C



Epoxide **VIII** can be prepared as outlined in Scheme 2C. Heating alkyl alcohol **IX** with epichlorohydrin or epibromohydrin and sodium hydride in DMF can afford epoxide **VIII**. In some cases compound **VIII** can be obtained from commercial resources. Examples of commercially available compounds of general structure **VIII** include glycidyl isopropyl ether, N butyl glycidyl ether, T butyl glycidyl ether and iso-butyl glycidyl ether.

Compound **V** can be prepared as described in Scheme 3C. Alkylation of compound **XII** with alkyl halides using t-BuLi as base can afford compound **XIII** as described by Pohlman et. al. (J. Org. Chem, (1997), 62, 1016-1022). Reduction of **XIV** using diborane can afford N-benzyl protected version of compound **V** after N-Boc deprotection with trifluoroacetic acid (TFA , for the diborane reduction see Jacobson et. al, J. Med. Chem, (1999), 42, 1123-1144).

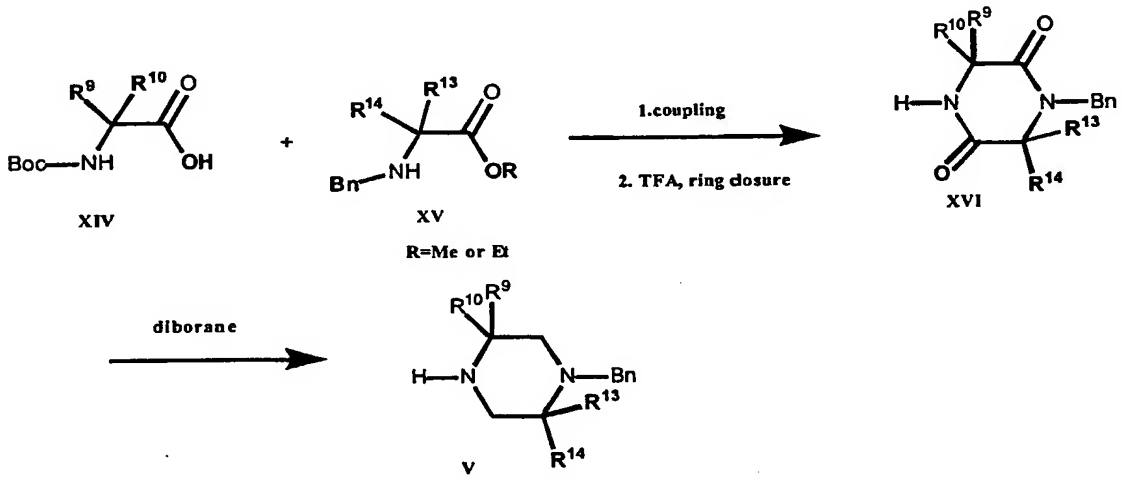
SCHEME 3C



XI XII XIII V

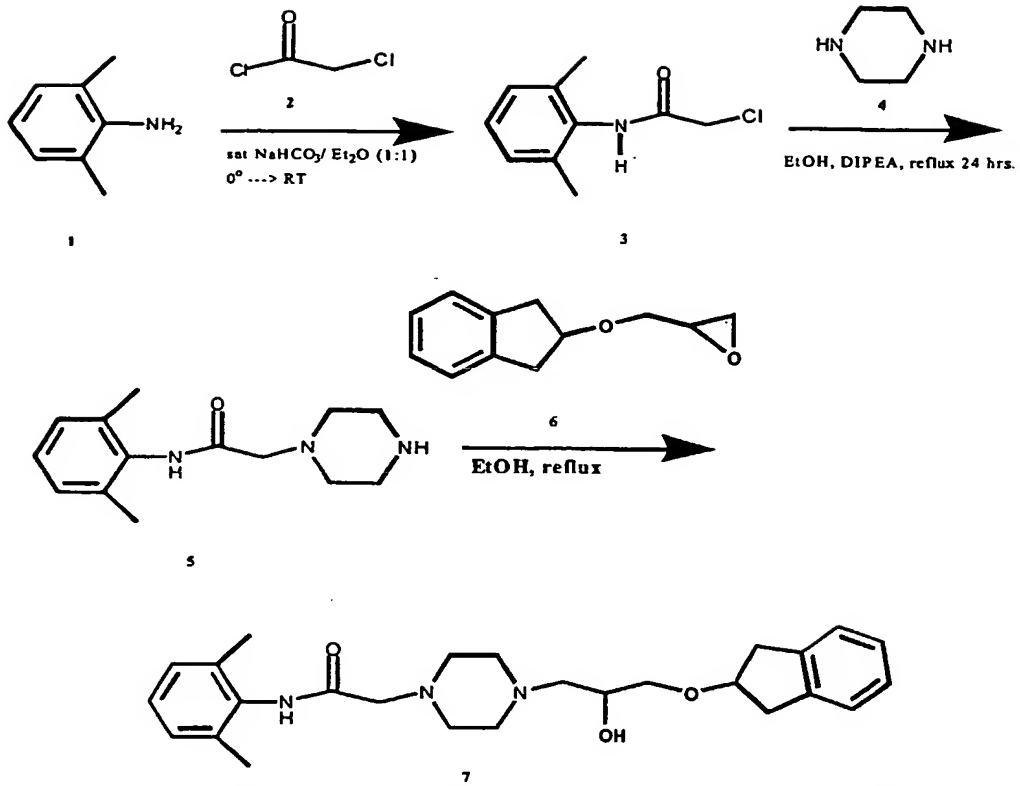
Compound V can also be prepared through standard coupling (eg. EDC or PyBroP) of D or L amino acids as outlined in Scheme 4C [For preparations of diketopiperazines see – P. Cledera et al. Tetrahedron, (1998) p. 12349-12360 and R. A. Smith et al Bioorg. Med. Chem. Lett. (1998) p. 2369-2374]. Reduction of the diketopiperazine with diborane can afford the N-benzyl protected version of compound V.

SCHEME 4C



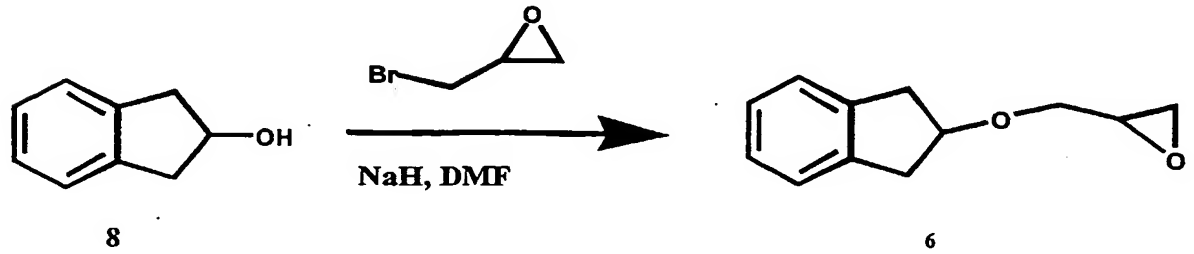
XIV XV R=Me or Et XVI V

A specific example of the preparation of a compound from this invention is disclosed in Schemes 5C and 6C to further illustrate how to prepare the compounds of this invention.



In particular, 2,6-dichloroaniline was acylated with 2-chloroacetyl chloride **2** using saturated bicarbonate and ether (1:1) as base and co-solvent, respectively to afford the chloroacetamide derivative **3**. Further reaction of compound **3** with piperazine afforded compound **5** through warming in ethanol. Reaction of compound **5** with epoxide **6** by warming both components in ethanol at reflux afforded piperazine derivative **7**. Compound **6** in turn was prepared by warming epibromohydrin with 2-indanol in DMF in presence of NaH as described in Scheme 6C.

SCHEME 6C



The acid addition salts of the compounds of this invention may be converted to the corresponding free base by treating with a suitable base, such as potassium carbonate or sodium hydroxide, typically in the presence of aqueous solvent, and at a temperature of between about 0 degrees C and 100 degrees C. The free base form is isolated by conventional means, such as extraction with an organic solvent.

Salts of the compounds of this invention may be interchanged by taking advantage of differential solubilities and volatilities, or by treating with the appropriately loaded ion exchange resin. This conversion is carried out at a temperature between about 0°C and the boiling point of the solvent being used as the medium for the procedure. Administration of the active compounds and salts described herein can be via any of the accepted modes of administration for therapeutic agents. These methods include oral, parenteral, transdermal, subcutaneous and other systemic modes. The preferred method of administration is oral, except in those cases where the subject is unable to ingest, by himself, any medication. In those instances it may be necessary to administer the composition parentarally.

Depending on the intended mode, the compositions may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, or the like, preferably in unit dosage forms suitable for single administration of precise dosages. The compositions may include one or more conventional pharmaceutical excipients and at least one active compound of this invention or the pharmaceutically acceptable salts thereof and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, etc.

The amount of active compound administered will, of course, be dependent on the subject being treated, the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician. However, an effective dosage is in the range of 0.1-30 mg/kg/day, preferably 0.5-20 mg/kg/day. For an average 70 kg human, this would amount to 7-2100 mg per day, or preferably 35-1400 mg/day. Since many of the effects of the compounds herein (protect skeletal muscles against damage resulting from trauma; protect skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication; treat shock conditions; preserve donor tissue and organs used in transplants; and treat cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, exercise induced angina, congestive heart disease, and myocardial infarction) are achieved through a similar mechanism (partial

fatty acid oxidation inhibition) dosages (and forms of administration) are all generally within the same general and preferred ranges for all these utilities.

For solid compositions, conventional non-toxic solid include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like may be used. The active compound as defined above may be formulated as suppositories using, for example, polyalkylene glycols, for example, propylene glycol, as the carrier. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound as defined above and optional pharmaceutical adjuvants in a excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound(s), a therapeutically effective amount, i.e. in an amount effective to alleviate the symptoms of the subject being treated. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium, carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain 10%-95% active ingredient, preferably 1-70%.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

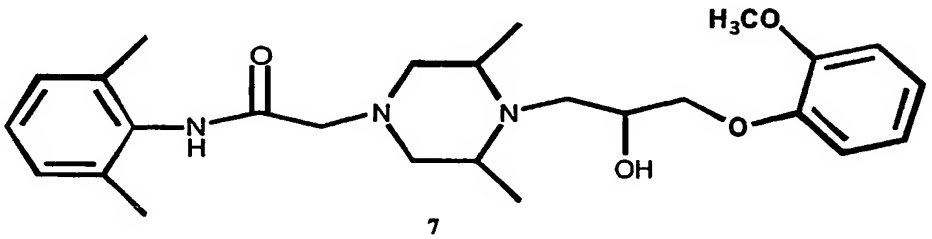
A more recently devised approach for parenteral administration employs the implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained. See, e.g., U.S. Pat. No. 3,710,795, which is incorporated herein by reference. In another recent approach, the compositions of this invention can be administered orally in a sustained release dosage form using the compositions and/or methods disclosed in U.S. Patent Application Serial No. 09/321,522, filed on May 27, 1999, the specification of which is incorporated herein by reference.

It is within the scope of this invention to administer one or more compounds of this invention to a mammal, and preferably to a human by other known routes of pharmaceutical dosage form administration including, but not limited to by bolus, intravenously, transdermally, through inhalation, sub-cutaneously, or any other therapeutic agent administration method or route know to one skilled in the art.

The following Examples are representative of the invention, but are not to be construed as limiting the scope of the claims.

Example 1

N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxy)propyl]-3,5-dimethylpiperazinyl}acetamide (7).



7

Part A.

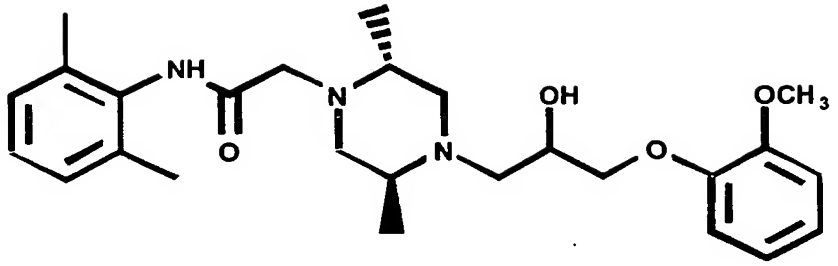
Synthesis of N-(2,6-dimethylphenyl)-2-chloroacetamide (3).

2,6-dimethylaniline (9.8 g, 81.2 mmol) was dissolved in ether (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) and the reaction mixture was cooled in an ice/water bath. To the cold solution was added chloroacetyl chloride 2 (9.17 g, 81.2 mmol) dropwise over a period of 2 h. The mixture was allowed to warm to RT over 14 h. The mixture was extracted with EtOAc (3 X 50). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was triturated in ether and filtered to afford compound 3 as a white solid.

Part B.

Synthesis of N-(2,6-dimethylphenyl)-2-(3,5-dimethylpiperazinyl)acetamide (5).

To a solution of compound 3 (5 g, 25.2 mmol) in ethanol (100 mL) was added 2,6-dimethylpiperazine 4 (2.1 g, 25.0 mmol) and N,N-diisopropylamine (3.2 g, 25.2 mmol). The reaction mixture was refluxed for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (10:1, DCM: MeOH) to afford compound 5.



Part C.

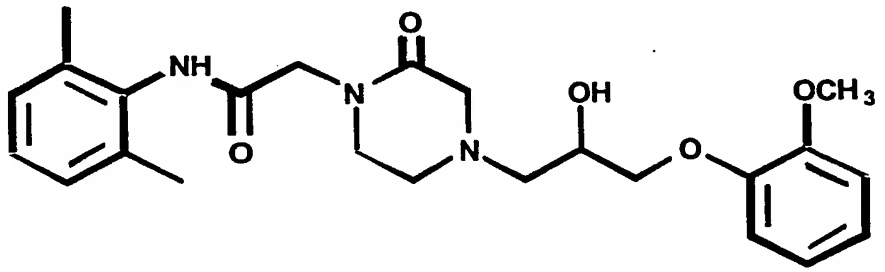
Synthesis of glycidyl 4-methoxyphenyl ether (6).

2-methoxyphenol (1.0 g, 8.0 mmol) and epichlorohydrin (3.7 g, 40.0 mmol) were dissolved in acetone (20 mL). K_2CO_3 (2.2 g, 16.0 mmol) was added and the mixture was heated at 70 °C for 24 h. The reaction mixture was concentrated in vacuo. The residue was dissolved 100 mL of EtOAc , washed with 100 mL water, dried over $MgSO_4$ and filtered. The mixture was evaporated to dryness and the residue was purified using column chromatography (2:1, hexane: ethyl acetate) to afford compound 6.

Part D.

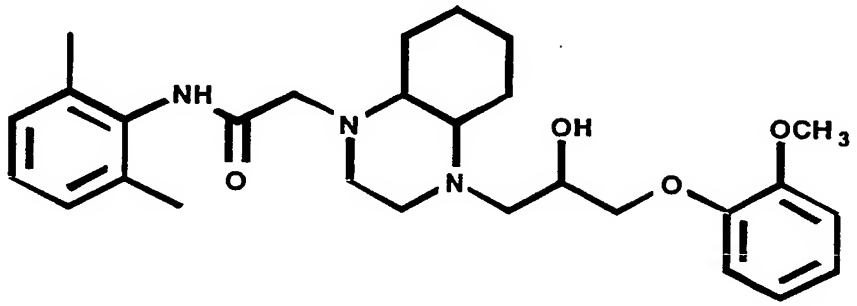
Synthesis of N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxy)propyl]-3,5-dimethylpiperazinyl}acetamide (7).

To a solution of compound 5 in 10 mL EtOH (0.4 g, 1.4 mmol) was added compound 6 (0.27 g, 1.5 mmol). The reaction mixture was refluxed for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by using Prep. TLC (10:1, DCM:MeOH) to afford compound 7.



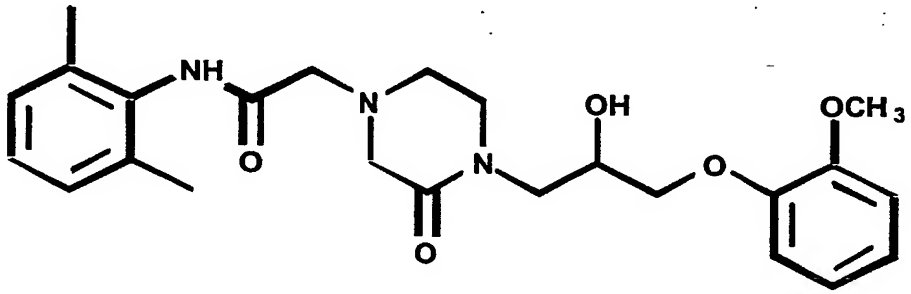
2-{(5S,2R)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-2,5-dimethylpiperazinyl}-N-(2,6-dimethylphenyl)acetamide (15)

Compound **15** was prepared in the manner of compound **7** substituting (2R, 5S)-dimethylpiperazine for 2,6-dimethylpiperazine 4 in part B to afford compound **15**: Mass spectrum (M+1) = 456.4.



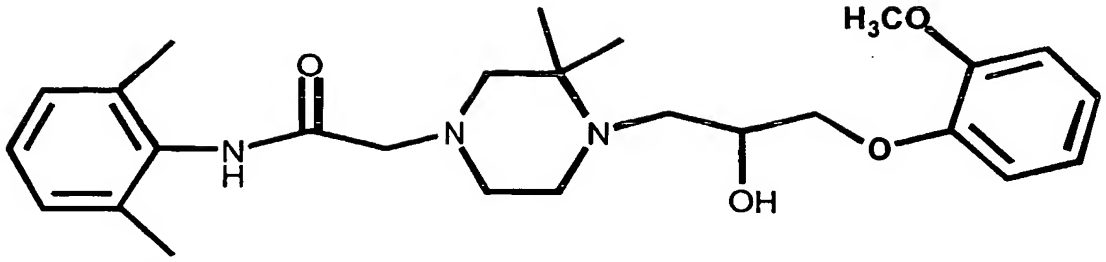
N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-2-oxopiperazinyl}acetamide (16)

Compound **16** was prepared substituting 4-benzyloxycarbonyl-2-oxo-piperazine for 2,6-dimethylpiperazine 4 in part B of compound **7** that was carried on to the final target in the manner of compound **7** after removal of the CBZ protecting group (hydrogenation – 20 psi, 10% palladium on carbon) to afford compound **16**: Mass spectrum (M+1) = 442.41.



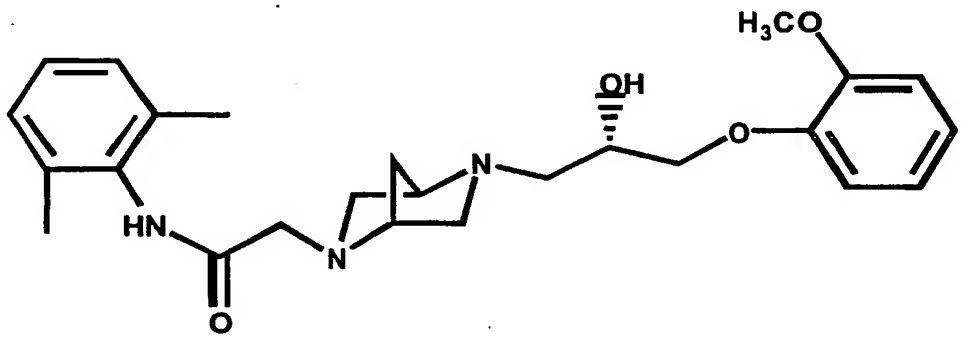
2,5-diaza-5-[2-hydroxy-3-(2-methoxyphenoxy)propyl]bicyclo[4.4.0]dec-2-yl}-N-(2,6-dimethylphenyl)acetamide (17)

Compound **17** was prepared in the manner of compound **7** substituting perhydroquinoxaline for 2,6-dimethylpiperazine 4 in part B to afford compound **15**: Mass spectrum (M+1) = 482.4.



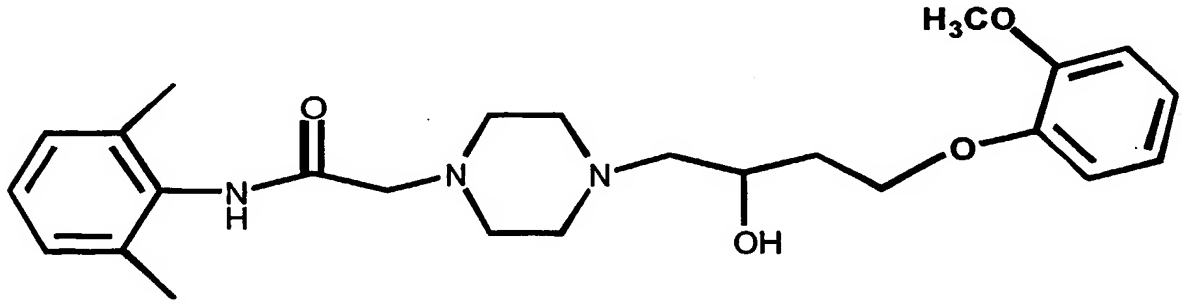
N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3,3-dimethylpiperazinyl}acetamide (18)

Compound **18** was prepared in the manner of compound **7** substituting 2,2-dimethylpiperazine for 2,6-dimethylpiperazine 4 in part B to afford compound **18**: Mass spectrum (M+1) = 456.51



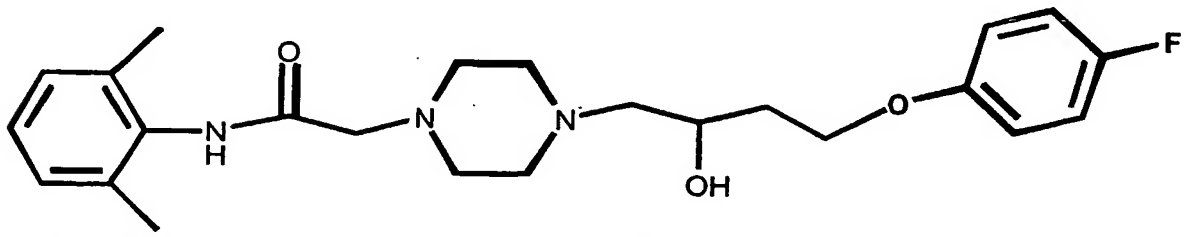
2-{5-[(2S)-2-hydroxy-3-(2-methoxyphenoxy)propyl](1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl}-N-(2,6-dimethylphenyl)acetamide (19)

Compound **19** was prepared in the manner of compound **7** substituting (1S,4S)-(+)-2,5-Diazabicyclo[2.2.1]heptane for 2,6-dimethylpiperazine 4 in part B to afford compound **19**: Mass spectrum (M+1) = 481.5

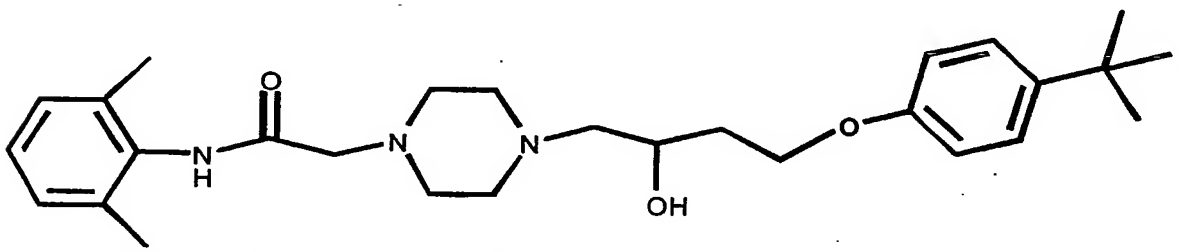


N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-4-(2-methoxyphenoxy)butyl]-piperazinyl}acetamide (20)

Compound **20** was prepared in the manner of compound **7** substituting 4-bromo-1,2-epoxybutane **6b** for epichlorohydrin **6a** in part B to afford compound **20**: Mass spectrum (M+1) = 442.37

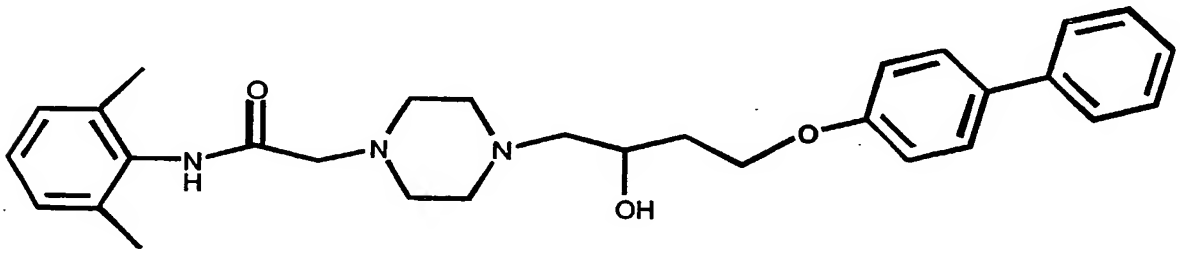


N-(2,6-dimethylphenyl)-2-{4-[4-(4-fluorophenoxy)-2-hydroxybutyl]-piperazinyl}acetamide (21) Compound **21** was prepared in the manner of compound **7** substituting 4-bromo-1,2-epoxybutane **6b** for epichlorohydrin **6a** in part B to afford compound **21**: Mass spectrum (M+1) = 430.35



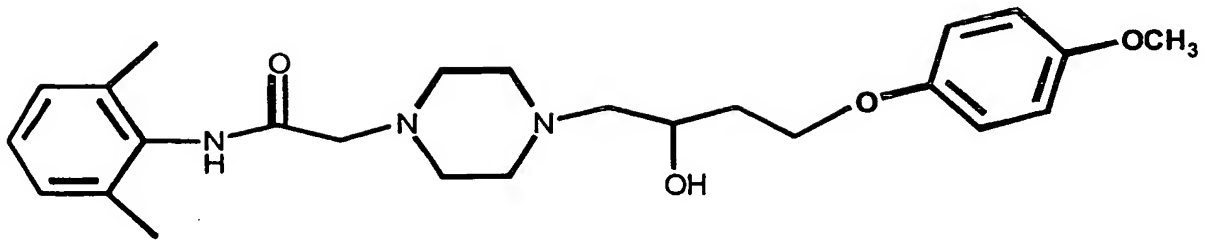
2-(4-{4-[4-(tert-butyl)phenoxy]-2-hydroxybutyl}piperazinyl)-N-(2,6-dimethylphenyl) acetamide (22)

Compound **22** was prepared in the manner of compound **7** substituting 4-bromo-1,2-epoxybutane **6b** for epichlorohydrin **6a** in part B to afford compound **22**: Mass spectrum (M+1) = 468.32



N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-4-(4-phenylphenoxy)butyl] piperazinyl}acetamide (23)

Compound **23** was prepared in the manner of compound **7** substituting 4-bromo-1,2-epoxybutane **6b** for epichlorohydrin **6a** in part B to afford compound **23**: Mass spectrum (M+1) = 488.41



N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-4-(4-methoxyphenoxy)butyl]-piperazinyl}acetamide (24)

Compound **24** was prepared in the manner of compound **7** substituting 4-bromo-1,2-epoxybutane **6b** for epichlorohydrin **6a** in part B to afford compound **24**: Mass spectrum (M+1) = 442.37

Example 2

N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3-oxopiperazinyl}acetamide (14)

Part E.

Synthesis of **(tert-butoxy)-N-(2-{[2-hydroxy-3-(2- methoxyphenoxy)propyl]amino} ethyl)carboxamide (11).**

Epoxide 6 (1.0 g, 5.5 mmol) and Boc-ethylenediamine (0.88 g, 5.5 mmol) were dissolved in 20 mL EtOH and the mixture was heated at reflux for 24 h. The solvent was evaporated and the residue was purified using column chromatography (1:1, Hex:EtOAc) to afford compound **11**.

Synthesis of **N-{2-[(tert-butoxy)carbonylamino]ethyl}-2-chloro-N[2-hydroxy-3-(2-methoxyphenoxy)propyl]acetamide (12)**

Compound 11 (1.0 g, 3.0 mmol) was dissolved in 20 mL DCM and treated with diisopropylethyl amine (0.76 g, 4.5 mmol). The mixture was cooled to °C. To the cold mixture was added dropwise chloroacetyl chloride in 5 mL DCM. The reaction mixture was allowed to stir at RT for 24 h. The mixture was diluted with 50 mL DCM and washed with 50 mL of water and 10% citric acid. The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was crystallized from ethylether to afford compound 12.

Synthesis of **1-[2-hydroxy-3-(2-methoxyphenoxy)propyl]piperazin-2-one (13).**

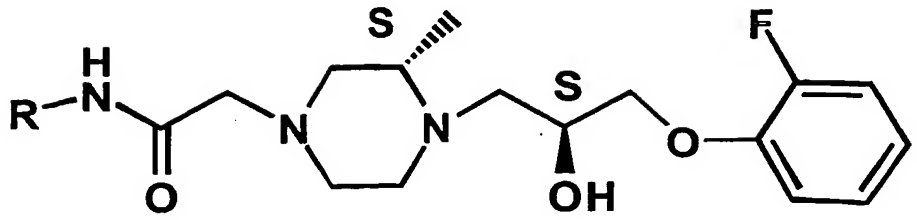
Compound 12 (0.5 g, 1.5 mmol) was dissolved in 10 mL TFA. The mixture was allowed to stir at RT for 2 h. TFA was removed under reduced pressure. The residue was dissolved in 20 mL EtOH and treated with diisopropylethyl amine (0.76 g, 4.5 mmol). The mixture was heated at reflux for 24 h. The solvent was removed under reduced pressure to afford compound 13 which was used without further purification.

Part F.

Synthesis of **N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3-oxopiperazinyl}acetamide (14)**

To a solution of compound **13** in 10 mL EtOH (0.1 g, 0.30 mmol) was added compound **3** (0.7 g, 0.36 mmol) and diisopropylethyl amine (0.76 g, 0.36 mmol). The reaction mixture was heated at reflux for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by using Prep. TLC (10:1, DCM:MeOH) to afford compound **14**: Mass spectrum (M+1) = 442.34

Example 3



The compounds listed in Table 1, below were made in the manner of compound 14 of Example 2.

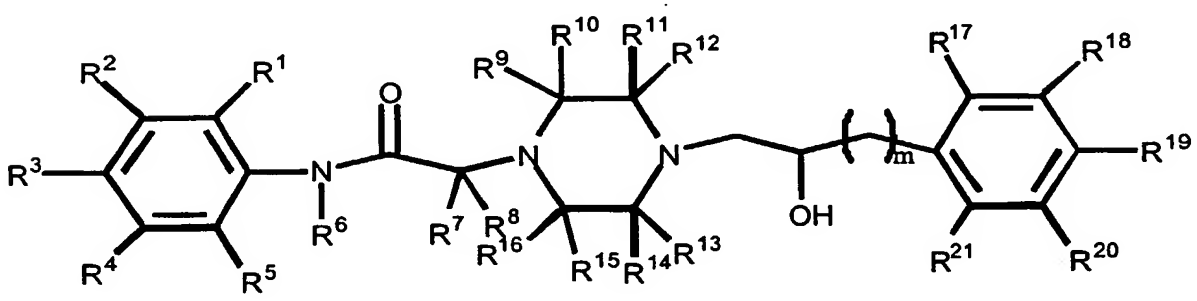
Table 1

	R	MH^+
25	2,6-dimethylphenyl	430.3
26	2,6-dichlorophenyl	471
27	4-aminosulfonylphenyl	481.2
28	3-trifluoromethyl-5methoxyphenyl	500.2
29	5-indanyl	442.2
30	1-naphthyl	452.3
31	1-(4-chloronaphthyl)	486.3
32	2-N-pyrrolyl-phenyl	467.3
33	Phenyl	402.2
34	2-chlorophenyl	436.2
35	2-chloro-4-methylphenyl	450.2
36	2-(1-methylethenyl)phenyl	442.3
37	2-methylphenyl	416.2
38	2-isopropyl-6-methylphenyl	458.4
39	3-methylthiophenyl	448.2
40	2-methoxy-4-chloro-5-methylphenyl	480.2
41	4-dimethylaminophenyl	445.3
42	2,4-dimethoxyphenyl	462.3
43	3,4-dichlorophenyl	471.1
44	4-chlorophenyl	436.3
45	3-chlorophenyl	436.2
46	3,5-dichlorophenyl	471.1
47	4-methoxyphenyl	432.3
48	4-methylphenyl	416.2
49	3-methylphenyl	416.2
50	4-fluorophenyl	420.2
51	4-cyanophenyl	427.3
52	4-acetylphenyl	444
53	2-methoxyphenyl	432.4
54	4-trifluoromethylphenyl	470.2
55	3-trifluoromethyl-4-chlorophenyl	504.1
56	3,5-dimethoxyphenyl	462.3
57	4-N-morpholinylphenyl	487.4
58	3-fluoro-4-methoxyphenyl	450.2

59	3,4,5-trimethoxyphenyl	492.3
60	3,4-dimethoxyphenyl	490
61	2-fluoro-4-chlorophenyl	454.2
62	2-hydroxymethyl-6-methylphenyl	446

(trifluoromethyl)phenyl] acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3,5-dimethoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-morpholin-4-ylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3-fluoro-4-methoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3,4,5-trimethoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3,4-dimethoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-chloro-2-fluorophenyl) acetamide, and 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[2-(hydroxymethyl-6-methylphenyl] acetamide.

34. A substituted piperazine compound having the following formula:



I

wherein m = or 1 or 2 or 3;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22};

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen or C_{1-15} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, CO_2R_{23}, $CON(R_{23})_2$, C_{1-4} alkyl, or aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ or aryl, wherein R^9 and R^{10} may together

form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl wherein R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a bridging ring system wherein the two R groups together comprise of from 1 to 4 carbon atoms and wherein R^9 and R^{10} or R^{11} and R^{12} or R^{13} and R^{14} or R^{15} and R^{16} may join to form a spiro ring system wherein the two R groups together comprise of from 1 to 5 carbon atoms;

R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22} and wherein R^{17} and R^{18} or R^{18} and R^{19} or R^{19} and R^{20} or R^{20} and R^{21} may combine to form a saturated ring including from 5 to 6 carbon atoms wherein from 0 to 2 carbon atoms may be substituted with an oxygen atom and wherein R^{17} and R^{18} may together form -CH=CH-CH=CH-;

R_{22} is selected from the group consisting of C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, or heteroaryl; and

R_{23} is selected from the group consisting of H, C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, mono- or dialkylamino, alkyl, CN, -O-C_{1-6} alkyl, or CF_3.

35. The compound of claim 34 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, heterocyclyl, aryl, and heteroaryl;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen or C_{1-8} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, CO_2R_{23}, $CON(R_{23})_2$, C_{1-4} alkyl, or aryl, wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl wherein R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a bridging ring system wherein the two R groups together comprise of from 1 to 4 carbon atoms ;

R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-15} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, and wherein R^{17} and R^{18} or R^{18} and R^{19} or R^{19} and R^{20} or R^{20} and R^{21} may combine to form a saturated ring including from 5 to 6 carbon atoms wherein from 0 to 2 carbon atoms may be substituted with an oxygen atom and wherein R^{17} and R^{18} may together form -CH=CH-CH=CH-;

R_{22} is selected from the group consisting of C_{1-8} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, CN, CF_3,; and

R_{23} is selected from the group consisting of H, C_{1-8} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, alkyl, CN, or CF_3.

36. The compound of claim 34 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, C_{1-8} alkyl, aryl, and heteroaryl;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen or C_{1-5} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, or aryl, wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl wherein R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a bridging ring system wherein the two R groups together comprise of from 1 to 2 carbon atoms ;

R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, C_{1-8} alkyl, aryl, and heteroaryl, and R^{19} and R^{20} may combine to form a saturated ring including from 5 carbon atoms wherein 2 carbon atoms may be substituted with an oxygen atom and wherein R^{17} and R^{18} may together form -CH=CH-CH=CH-;

R_{22} is selected from the group consisting of C_{1-6} alkyl, aryl; and

R_{23} is selected from the group consisting of H, C_{1-6} alkyl, aryl;

37. The composition of claim 34 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, C_{1-6} alkyl;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen or C_{1-3} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, C_{1-3} alkyl, wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl wherein R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a bridging ring system wherein the two R groups together comprise of from 1 to 2 carbon atoms ;

R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, C_{1-6} alkyl, and R^{19} and R^{20} may combine to form a saturated ring including from 5 carbon atoms wherein 2 carbon atoms may be substituted with an oxygen atom and wherein R^{17} and R^{18} may together form -CH=CH-CH=CH-;

R_{22} is selected from the group consisting of C_{1-3} alkyl; and

R_{23} is selected from the group consisting of H, C_{1-3} alkyl;

38. The compound of claim 37 wherein m = 1 or 2 or 3.

39. The compound of claim 37 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, methyl, wherein R^9 and R^{10} may together form a carbonyl, R^{13} and R^{14} may together form a carbonyl, wherein R^{11} and R^{13} or R^9 and R^{15} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a bridging ring system wherein the two R groups together comprise of from 1 to 2 carbon atoms.

40. The compound of claim 37 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, and methyl.

41. The compound of claim 39 or 40 wherein R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and methyl. .

42. The compound of claim 37 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are hydrogen.

43. The compound of claim 37 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, C_{1-2} alkyl;

R^6 is hydrogen; and

R^7 and R^8 each independently selected from the group consisting of hydrogen or methyl; and

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, C_{1-3} alkyl, wherein R^9 and R^{10} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl;

R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, C_{1-6} alkyl, and R^{19} and R^{20} may combine to form a saturated ring including from 5 carbon atoms wherein 2 carbon atoms may be substituted with an oxygen atom and wherein R^{17} and R^{18} may together form -CH=CH-CH=CH-;

R_{22} is selected from the group consisting of methyl; and

R_{23} is selected from the group consisting of H, methyl;

44. The compound of claim 43 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, and methyl.

45. The compound of claim 43 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are hydrogen.

46. The compound of claim 43 wherein R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, OR_{23}, C_{1-4} alkyl, and R^{19} and R^{20} may combine to form a saturated ring including from 5 carbon atoms wherein 2 carbon atoms may be substituted with an oxygen atom and wherein R^{17} and R^{18} may together form -CH=CH-CH=CH-.

47. The compound of claim 43 wherein R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, OR_{23}, C_{1-4} alkyl, and R^{19} and R^{20} may combine to form $-O-CH_2-O-$ or $-OCH_2CH_2O-$ and wherein R^{17} and R^{18} may together form -CH=CH-CH=CH-;

48. The compound of claim 34 wherein m = 1 or 2;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-2} alkyl wherein R_{22} is a C_{1-2} alkyl;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and methyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen and C_{1-2} alkyl, or R^9 and R^{10} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl wherein R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join to form a ring including from 1 to 4 carbon atoms; and

R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from the group consisting of hydrogen, halo, OR_{23}, C_{1-3} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, heterocyclyl, aryl, and heteroaryl,

wherein R_{23} is C_{1-2} alkyl and wherein R^{17} and R^{18} or R^{18} and R^{19} may together form a ring selected from the group consisting of -CH=CH-CH=CH-, -O-CH_2-O, and –O-CH_2-CH_2-O-.

49. The compound of claim 48 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, and methyl.

50. The compound of claim 48 wherein R^6, R^7 and R^8 are each hydrogen.

51. The compound of claim 48 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl.

52. The compound of claim 48 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen and methyl.

53. The compound of claim 15 wherein R^9 and R^{10} together form a carbonyl, R^{15} and R^{16} together form a carbonyl or both R^9 and R^{10} together form a carbonyl and R_{15} and R^{16} together form a carbonyl.

54. The compound of claim 48 wherein R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl and OR^{22} wherein R_{22} is C_{1-2} alkyl.

55. The compound of claim 48 wherein R^{17} and R^{18} or R^{18} and R^{19} together form a ring selected from the group consisting of -CH=CH-CH=CH-, -O-CH_2-O.

56. The compound of claim 34 wherein

m = 1 or 2;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, and methyl;

R^6, R^7 and R^8 are each hydrogen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl, or R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl and wherein R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join to form a ring including from 1 to 4 carbon atoms;

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, CF_3 and OR^{22}; and

R_{22} is C_{1-2} alkyl.

57. The compound of claim 56 wherein R^1 and R^5 are each methyl and R^2, R^3, and R^4 are each hydrogen.

58. The compound of claim 56 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen or methyl.

59. The compound of claim 56 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each hydrogen.

60. The compound of claim 56 wherein, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each selected from the group consisting of hydrogen, Cl, F, $-OCH_3$, $-CF_3$ and C_{1-4} alkyl.

61. The compound of claim 60 wherein R^{18}, and R^{20} are each hydrogen.

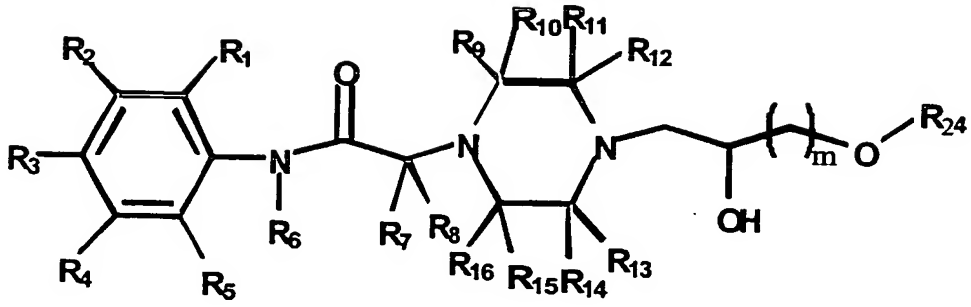
62. The compound of claim 60 wherein R^{19} is $-OCH_3$.

63. The compound of claim 56 wherein, R^{17} is $-OCH_3$, and R^{18}, R^{19}, R^{20} and R^{21} are each hydrogen.

64. The compound of claim 56 wherein, R^{17}, R^{18}, R^{20} and R^{21} are each hydrogen and R^{19} is selected from the group consisting of $-OCH_3$, -F, CF_3, C_{1-4}.

65. A substituted piperazine compound of claim 34 selected from the group consisting of: N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-4-phenylbutyl)piperazinyl]acetamide; N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenyl)propyl]piperazinyl}acetamide; 2-[4-(3-(2H-benzo[d]1,3-dioxolen-5-yl)-2-hydroxypropyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide; N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(4-methoxyphenyl)propyl]piperazinyl}acetamide; N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-phenylpropyl]piperazinyl}acetamide; N-(2,6-dimethylphenyl)-2-{4-[4-(4-methoxyphenyl)-2-hydroxybutyl]piperazinyl}acetamide, 2-{4-[4-(2,6-difluorophenyl)-2-hydroxybutyl]piperazinyl}-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-{4-[4-(2-chlorophenyl)-2-hydroxybutyl]piperazinyl}acetamide, 2-(4-{4-[4-(tert-butyl)phenyl]-2-hydroxybutyl}piperazinyl)-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-{4-[4-(2-fluorophenyl)-2-hydroxybutyl]piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-4-[4-(trifluoromethyl)phenyl]butyl}piperazinyl)acetamide, 2-[4-(3-(2H-benzo[d]1,3-dioxolen-5-yl)-2-hydroxypropyl)piperazinyl]-N-(2,6-dimethylphenyl)-2-methylpropanamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-phenylpropyl)piperazinyl]-2-methylpropanamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(3,4,5-trimethoxyphenyl)propyl]piperazinyl}-2-methylpropanamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-5-phenylpentyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-{4-[5-(2-fluorophenyl)- 2-hydroxy-pentyl]piperazinyl}acetamide, and N-(2,6-dimethylphenyl)-2-{4-[5-(2-chlorophenyl)- 2-hydroxy-pentyl]piperazinyl}acetamide.

66. A substituted piperazine compound having the following formula:



I

wherein m = 1, 2, or 3;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}SO_2R^{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, and SO_2R^{22} ;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen or C_{1-3} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, CO_2R^{20}, $CON(R^{20})_2$, C_{1-4} alkyl, or aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR^{20}, $N(R^{20})_2$, CO_2R^{20}, $CON(R^{20})_2$ or aryl, wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl with the proviso that R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a ring including from 1 to 3 carbon atoms;

R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to three substituents selected from the group consisting of halo, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, C_{1-2} alkyl, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl;

R^{20} is selected from the group consisting of H, C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, mono- or dialkylamino, alkyl, CN, -O-C_{1-6} alkyl, or CF_3; and

R^{22} is selected from the group consisting of C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, or heteroaryl.

67. The compound of claim 66 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $SO_2N(R^{20})_2$, CO_2R^{20}, $CON(R^{20})_2$, C_{1-8} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, or SO_2R^{22} ;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen or C_{1-3} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, $CON(R^{20})_2$, C_{1-4} alkyl, or wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl; and

R^{20} is selected from the group consisting of H, C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkylcyano, -O-C_{1-6} alkyl, or CF_3.

68. The compound of claim 66 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{20}, C_{1-5} alkyl, C_{2-3} alkenyl, or C_{2-3} alkynyl, wherein the alkyl substituent is optionally substituted with CF_3;

R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen or C_{1-3} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, $CON(R^{20})_2$, or C_{1-4} alkyl wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl;

R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to two substituents selected from the group consisting of halo, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, C_{1-2} alkyl, and aryl wherein the optional aryl substituent is optionally substituted with

from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl; and

R^{20} is selected from the group consisting of H, C_{1-8} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, -O-C_{1-3} alkyl, or CF_3.

69. The compound of claim 66 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{20}, C_{1-3} alkyl, C_{2-3} alkenyl, or C_{2-3} alkynyl, wherein the alkyl is optionally substituted with CF_3;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen or methyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen or C_{1-2} alkyl, wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl;

R_{24} is selected from the group consisting of alkyl , cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to two substituents selected from the group consisting of halo, CF_3, OR^{20}, $S(O)R^{22}$, C_{1-2} alkyl, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl; and

R^{20} is selected from the group consisting of H, C_{1-5} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, -OMe, or CF_3.

70. The compound of claim 66 wherein m = 1 or 2;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-4} alkyl and wherein R^{22} is a C_{1-3} alkyl;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and C_{1-3} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, $CON(R^{20})_2$, C_{1-4} alkyl, or aryl wherein the alkyl and aryl substituents are each optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, OR^{20}, $N(R^{20})_2$, $CON(R^{20})_2$ or aryl wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15}

and R^{16} may together form a carbonyl with the proviso that R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a ring;

R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to two substituents selected from the group consisting of halo, CF_3, OR^{20}, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl; and

R^{20} is selected from the group consisting of H, C_{1-3} alkyl, or aryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent individually selected from the group consisting of halo, -OMe, and CF_3.

71. The compound of claim 70 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl, or R^9 and R^{10} together form a carbonyl, or R^{11} and R^{12} together form a carbonyl, or R^{13} and R^{14} together form a carbonyl, or R^{15} and R^{16} together form a carbonyl, R^{10} and R^{11} together form $-CH_2CH_2CH_2CH_2-$.

72. The compound of claim 70 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, $CON(R^{20})_2$, C_{1-3} alkyl, or aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, $N(R^{20})_2$, and aryl or wherein R^9 and R^{10} may together form a carbonyl, or R^{11} and R^{12} may together form a carbonyl with the proviso that R^{11} and R^{13} or R^9 and R^{15} or R^9 and R^{11} or R^{11} and R^{15} or R^9 and R^{13} may join together to form a ring.

73. The compound of claim 70 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, or C_{1-2} alkyl, wherein the alkyl substituent is optionally substituted with 1 substituent selected from the group consisting of $N(R^{20})_2$, or aryl or wherein R^9 and R^{10} may together form a carbonyl.

74. The compound of claim 66 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{20}, or C_{1-3} alkyl wherein the alkyl substituent is optionally substituted with CF_3.

75. The compound of claim 66 wherein R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen or methyl.

76. The compound of claim 66 wherein m=1.

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, CF_3, OR^{20}, or C_{1-2} alkyl;

R^6, R^7 and R^8 are each hydrogen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen or C_{1-2} alkyl, or wherein R^9 and R^{10} may together form a carbonyl;

R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to two substituents selected from the group consisting of halo, CF_3, OR^{20}, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, phenyl, CF_3, OR^{20}, and C_{1-4} alkyl; and

R^{20} is selected from the group consisting of H or C_{1-3} alkyl.

77. The compound of claim 76 wherein R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, OR^{20}, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, phenyl, CF_3, OR^{20}, and C_{1-4} alkyl.

78 The compound of claim 66 wherein R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, OR^{20}, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, phenyl, CF_3, OR^{20}, and C_{1-4} alkyl.

79. The compound of claim 76 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OCH_3, or methyl.

80. The compound of claim 76 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, or methyl.

81. The compound of claim 76 wherein R^{11} and R^{15} are each selected from the group consisting of hydrogen or methyl, R^9, R^{10}, R^{12}, R^{13}, R^{14} and R^{16} are each hydrogen and R^9 and R^{10} may together form a carbonyl.

82. A compound of claim 66 wherein m = 1;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, or methyl;

R^6, R^7 and R^8 are each hydrogen;

R^{11} and R^{15} are each selected from the group consisting of hydrogen or methyl, R^9, R^{10}, R^{12}, R^{13}, R^{14} and R^{16} are each hydrogen and R^9 and R^{10} may together form a carbonyl;

R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, OR^{20}, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, phenyl, CF_3, OR^{20}, and C_{1-4} alkyl; and

R^{20} is methyl or H.

83. The compound of claim 82 wherein R_{24} is alkyl having from 1 to 6 carbon atoms and cycloalkyl.

84. The compound of claim 82 wherein R_{24} is a fused phenylcycloalkyl that is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, CF_3, OR^{20}, C_{1-2} alkyl, and aryl.

85. The compound of claim 82 wherein R_{24} is phenylmethyl that is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, CF_3, OR^{20}, C_{1-4} alkyl, and aryl.

86. The compound of claim 82 wherein R^2, R^3, and R^4 are each hydrogen and R^1 and R^5 are each methyl.

87. The compound of claim 66 wherein m=1;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen or methyl;

R^6, R^7 and R^8 each hydrogen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each hydrogen; and

R_{24} is selected from the group consisting of alkyl having from 1 to 6 carbon atoms, cycloalkyl having from 4 to 6 carbon atoms, fused phenylcycloalkylwith a phenyl that is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, CF_3, OH, methyl, and aryl, and aryl that is optionally substituted with from 1 to 2 substituents selected from the group consisting of halo, CF_3, OH, C_{1-2} alkyl, and aryl.

88. The compound of claim 66 selected from the group consisting of substituted piperazine compound selected from the group consisting of 2-({2-[4-(3-isopropoxy-2-hydroxypropyl)piperazinyl]- N-({2,6-dimethylphenyl)acetamide; N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indan-2-yloxypropyl)piperazinyl]acetamide; N-(2,6-dimethylphenyl)-2-{4-

[2-hydroxy-3-(phenylmethoxy)propyl]piperazinyl}acetamide, 2-({2-[4-(3-cyclopentyloxy-2-hydroxypropyl)piperazinyl]- N-({2,6-dimethylphenyl)acetamide, 2-({2-[4-(3-cyclohexyloxy-2-hydroxypropyl)piperazinyl]- N-({2,6-dimethylphenyl)acetamide, 2-[4-(3-{[4-(tert-butyl)phenyl]methoxy}-2-hydroxypropyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{3-[(2-fluorophenyl)methoxy]-2-hydroxypropyl}piperazinyl)acetamide, 2-(4-{3-[(2,4-difluorophenyl)methoxy]-2-hydroxypropyl}piperazinyl)-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-{[4-(trifluoromethyl)phenyl]methoxy}propyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(2-methoxyphenyl)methoxy]propyl}piperazinyl)acetamide, 2-(4-{3-[(2,4-dimethoxyphenyl)methoxy]-2-hydroxypropyl}piperazinyl)-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(4-methoxyphenyl)methoxy]propyl}piperazinyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{3-[(4-fluorophenyl)methoxy]-2-hydroxypropyl}piperazinyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(4-methylphenyl)methoxy]propyl}piperazinyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(4-phenylphenyl)methoxy]propyl}piperazinyl)acetamide, N-(2,6-dimethylphenyl)-2-(4-{3-[(4-butylphenyl)methoxy]-2-hydroxypropyl}piperazinyl)acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydoxy-3-(2-naphthylmethoxy)propyl]piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[3-(cyclohexylmethoxy)-2-hydroxypropyl]piperazinyl}acetamide, and N-(2,6-dimethylphenyl)-2-(4-{3-[(4-fluorophenyl)methoxy]-2-hydroxypropyl}-3,3-dimethylpiperazinyl)acetamide.

89. A method of treatment comprising administering a therapeutically effective amount of a compound of claim 1 to a mammal in need of a treatment selected from the group consisting of protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases, treating shock conditions, preserving donor tissue and organs used in transplants, or treating cardiovascular diseases.

90. The method of claim 89 wherein the cardiovascular disease is selected from the group consisting of atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, exercise induced angina, congestive heart disease, or myocardial infarction.

91. The method of claim 89 wherein the therapeutically effective amount ranges from about 0.01 to about 100 mg/kg weight of the mammal.

92. The method of claim 89 wherein the mammal is a human.

93. A pharmaceutical composition of matter comprising the compound of claim 1

and one or more pharmaceutical excipients.

94. The pharmaceutical composition of matter of claim 93 wherein the pharmaceutical composition is in the form of a solution.

95. The pharmaceutical composition of matter of claim 93 wherein the pharmaceutical composition is in a form selected from the group consisting of a tablet or a capsule.

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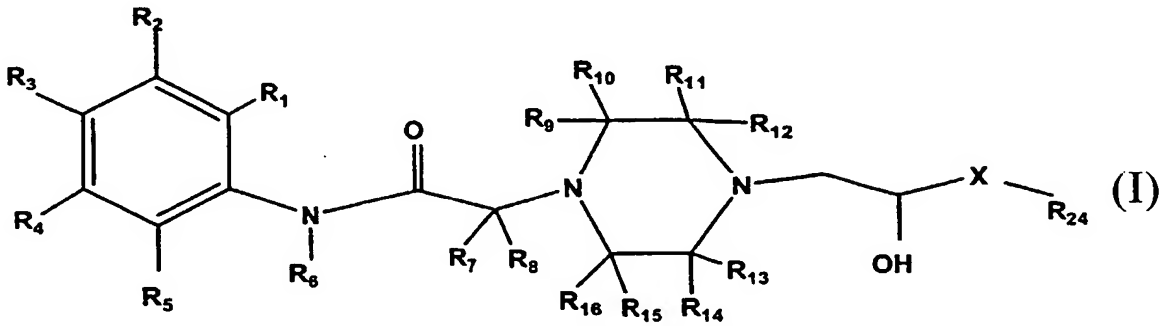
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED PIPERAZINE COMPOUNDS



(I)

(57) Abstract: Novel compounds of the general formula (I) and pharmaceutically acceptable acid addition salts thereof, wherein the compounds are useful in therapy to protect skeletal muscles against damage resulting from trauma or to protect skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, in the treatment of cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction.

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Int ional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D241/04 C07D241/08 C07D241/42 C07D295/108 C07D317/54
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 483 932 A (RICHTER GEDEON VEGYESZET) 6 May 1992 (1992-05-06) page 3, line 1 - line 22 ---	1-95
Y	EP 0 407 780 A (SYNTEX PHARMA LTD) 16 January 1991 (1991-01-16) claims 1-12,14,15 & US 5 506 229 A 9 April 1996 (1996-04-09) cited in the application ---	1-95
Y	US 4 567 264 A (KLUGE ARTHUR F ET AL) 28 January 1986 (1986-01-28) cited in the application abstract; claims --- -/--	1-95

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2001	31/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 01/05606

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ˜	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 015, no. 357 (C-0866), 10 September 1991 (1991-09-10) & JP 03 141258 A (KOWA CO), 17 June 1991 (1991-06-17) abstract	1-95
Y	-& JP 03 141258 A (KOWA CO) 17 June 1991 (1991-06-17) page 565, compounds 19 and 20	1-95
Y	US 4 766 125 A (VAN DAELE GEORGES) 23 August 1988 (1988-08-23) abstract; claims 1,2,8,13; tables	1-95
A	US 4 558 129 A (KLUGE ARTHUR F ET AL) 10 December 1985 (1985-12-10) abstract; claims	1-95
A	EP 0 143 016 A (CERM CENT EUROP RECH MAUVERNAY) 29 May 1985 (1985-05-29) abstract; claims	1-95

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (partly), 2-33, 53, 89-95

   Compounds of the formula as shown in claim 1 wherein at least one of R9, R10, R11, R12, R13, R14, R15 or R16 is not hydrogen, their pharmaceutical use and pharmaceutical compositions containing these compounds.

2. Claims: 1 (partly), 34-52, 54-65

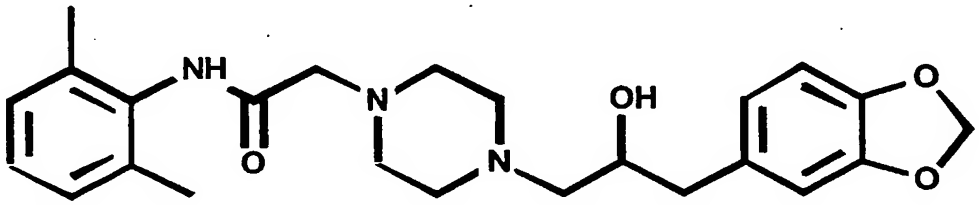
   Compounds of formula I as shown in claim 34 wherein the "right-hand" phenyl ring is not attached to the rest of the molecule via an oxygen atom, but via carbon atoms.

3. Claims: 1 (partly), 66-88

   Compounds of formula I as shown in claim 66 wherein the substituent R24 cannot be a non-fused phenyl ring.

Example 4

2-[4-(3-(2H-benzo[d]1,3-dioxolen-5-yl)-2-hydroxypropyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide (7B).



Part A.

Synthesis of N-(2,6-dimethylphenyl)-2-chloroacetamide (3B).

2,6-dimethylaniline (9.8 g, 81.2 mmol) was dissolved in ether (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) and the reaction mixture was cooled in an ice/water bath. To the cold solution was added chloroacetyl chloride **2B** (9.17 g, 81.2 mmol) dropwise over a period of 2 h. The mixture was allowed to warm to RT over 14 h. The mixture was extracted with EtOAc (3 X 50). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was triturated in ether and filtered to afford compound **3B** as a white solid.

Part B.

Synthesis of N-(2,6-dimethylphenyl)-2-piperazinylacetamide (5B).

To a solution of compound 3 (5 g, 25.2 mmol) in ethanol (100 mL) was added compound **4B** (2.1 g, 25.0 mmol) and N,N-diisopropylamine (3.2 g, 25.2 mmol). The reaction mixture was refluxed for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (10:1 dichloromethane: methanol) to afford compound **5B**.

Part C.

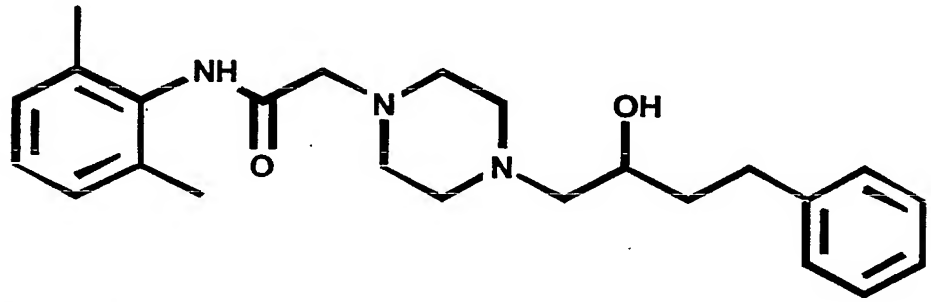
Synthesis of 5-(oxiran-2-ylmethyl)-2H-benzo[*d*]1,3-dioxane (6B).

To an ice cold solution of 8 (1.0 g, 6.17 mmol) in dichloromethane was added dropwise a solution of 3-chloroperoxybenzoic acid (1.8 g, 10.43 mmol) in 20 mL dichloromethane over a period of 1 h. The reaction mixture was allowed to stir at RT for 12 h. The reaction mixture was filtered to remove any solids and concentrated *in vacuo*. To the residue was added diethyl ether (200ml), and it was washed with saturated sodium bicarbonate (3x100ml). The organic layer was dried over $MgSO_4$, and concentrated *in vacuo* . The residue was purified using Prep. TLC (2:1 hexane: ethyl acetate) to yield **6B**.

Part D.

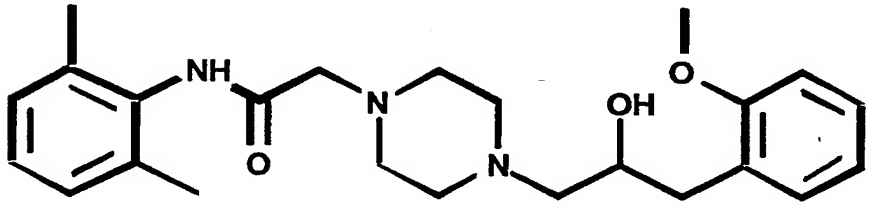
2-[4-(3-(2H-benzo[d]1,3-dioxolen-5-yl)-2-hydroxypropyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide (7B)

To a solution of compound **5B** (0.4 g, 1.64 mmol) in ethanol (100 mL) was added compound **6B** (0.38 g, 2.14 mmol) in 10 mL EtOH. The reaction mixture was refluxed for 24 h. The mixture was concentrated *in vacuo*, and the residue was purified by using Prep. TLC (10:1 dichloromethane: methanol) to afford compound **7B**: Mass spectrum (MH+1) = 426.34.



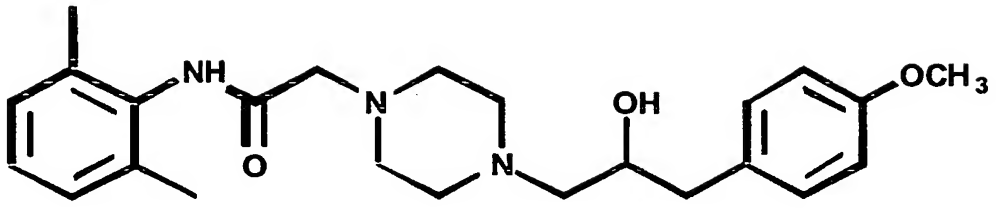
N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-4-phenylbutyl)piperazinyl]acetamide (9B).

Compound 9B was prepared in the manner of compound 7B substituting 4-phenyl-butene for 3-(3,4-methylendioxyphenyl)-1-propene in part C to afford compound **9B**: Mass spectrum (MH+1) = 396.32.



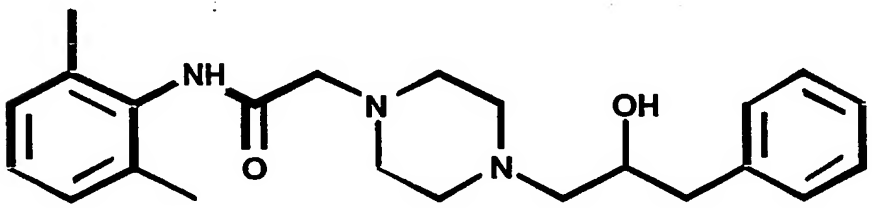
N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenyl)-propyl]piperazinyl}acetamide (10B)

Compound **10B** was prepared in the manner of compound **7B** substituting 3-(2-methoxyphenyl)-1-propene for 3-(3,4-methylendioxyphenyl)-1-propene in part C to afford compound **10B**: Mass spectrum (MH+1) = 412.35.



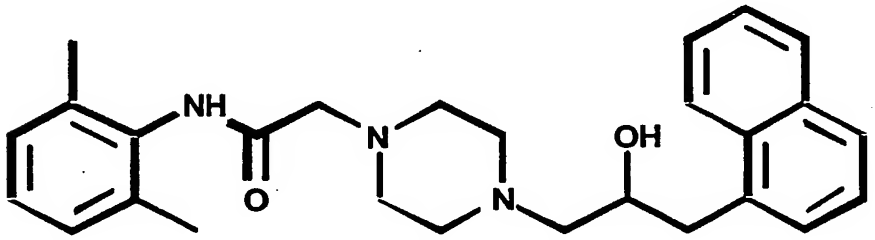
N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(4-methoxyphenyl)propyl]piperazinyl}acetamide (11B).

Compound **11B** was prepared in the manner of compound **7B** substituting 3-(4-methoxyphenyl)-1-propene for 3-(3,4-methylendioxyphenyl)-1-propene in part C to afford compound **11B**: Mass spectrum (MH+1) = 412.35.



N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-phenylpropyl]piperazinyl}acetamide (12B)

Compound **12B** was prepared in the manner of compound **7B** substituting 3-phenyl-1-propene for 3-(3,4-methylendioxyphenyl)-1-propene in part C to afford compound **12B**:
Mass spectrum (MH+1) = 382.



N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-naphthylpropyl)piperazinyl]acetamide (13B).

Compound **13B** was prepared in the manner of compound **7B** substituting 3-(1-naphthyl)-1-propene for 3-(3,4-methylendioxyphenyl)-1-propene in part C to afford compound **13**:Mass spectrum (MH+1) = 432.55.

EXAMPLE 5

Part A

Intermediate (14B): To a solution of 4-methoxybenzyl chloride (2-mmol) in anhydrous ether (10 mL), was added allylmagnesium bromide (4 mL, 1M solution in THF) and the reaction mixture was allowed to stir for 16h at room temperature. Sat. ammonium chloride solution 91mL) was added and the ether layer was separated, washed with water and dried. Evaporation of ether under reduced pressure afforded olefin **14B** as an oil. It was used in the next reaction without purification.

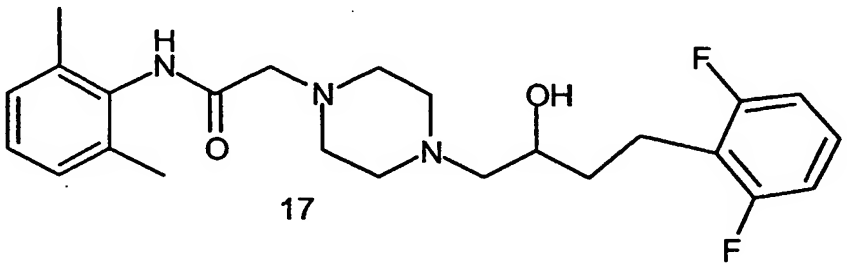
Part B

Intermediate (15B): To an ice cold solution of **15B** (2 mmol) in dichloromethane was added dropwise a solution of 3-chloroperoxybenzoic acid (4 mmol) in 20 mL dichloromethane over a period of 1 h. The reaction mixture was allowed to stir at RT for 12 h. The reaction mixture was filtered to remove any solids and concentrated *in vacuo*. To the residue was added diethyl ether (200ml), and it was washed with saturated sodium bicarbonate (3x100ml). The organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified using Prep. TLC (2:1 hexane: ethyl acetate) to yield **15B**.

Part C

Synthesis of N-(2,6-dimethylphenyl)-2-{4-[4-(4-methoxyphenyl)-2-hydroxybutyl]piperazinyl}acetamide(16B)

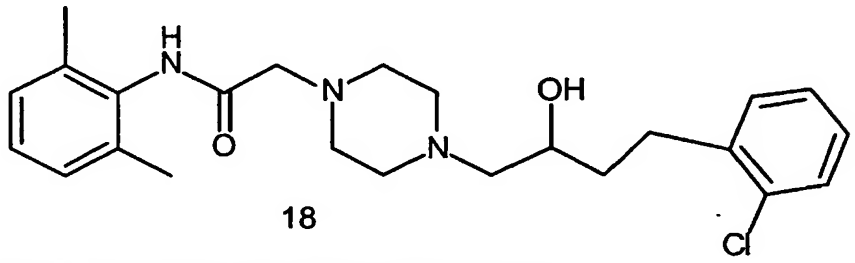
To a solution of compound **5B** (0.4 g, 1.64 mmol) in ethanol (100 mL) was added compound **15B** (2.14 mmol) in 10 mL EtOH. The reaction mixture was refluxed for 24 h. The mixture was concentrated *in vacuo*, and the residue was purified by using Prep. TLC (10:1 dichloromethane: methanol) to afford compound **16.** (M+1) = 426.3



17

2-{4-[4-(2,6-difluorophenyl)-2-hydroxybutyl]piperazinyl}-N-(2,6-dimethylphenyl)acetamide(17B)

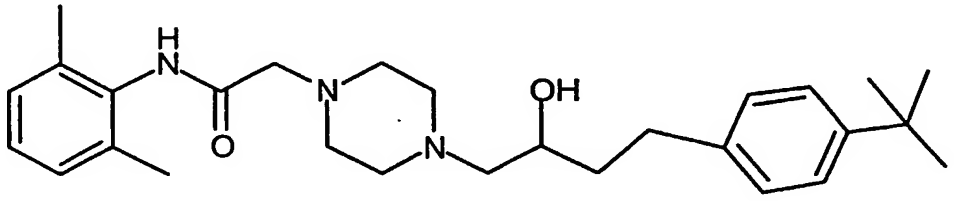
Compound **17B** was prepared in a manner similar to that of compound **16B** substituting 2,6-difluorobenzyl chloride for 4-methoxybenzyl chloride. (M+1) 432.2



18

N-(2,6-dimethylphenyl)-2-{4-[4-(2-chlorophenyl)-2-hydroxybutyl]piperazinyl}acetamide(18B)

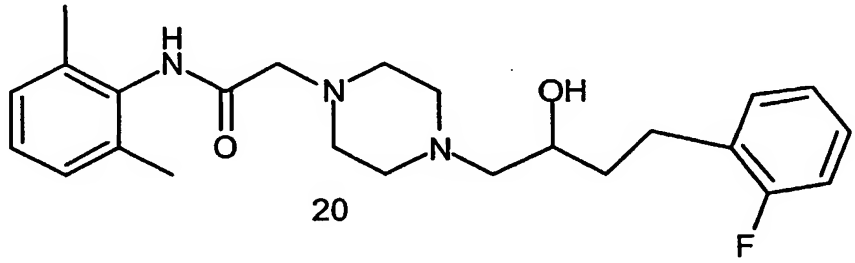
Compound **18B** was prepared in a manner similar to that of compound **16B** substituting 2-chlorobenzyl chloride for 4-methoxybenzyl chloride. (M+1) = 430.2



19

2-(4-{4-[4-(tert-butyl)phenyl]-2-hydroxybutyl}piperazinyl)-N-(2,6-dimethylphenyl)acetamide(19B)

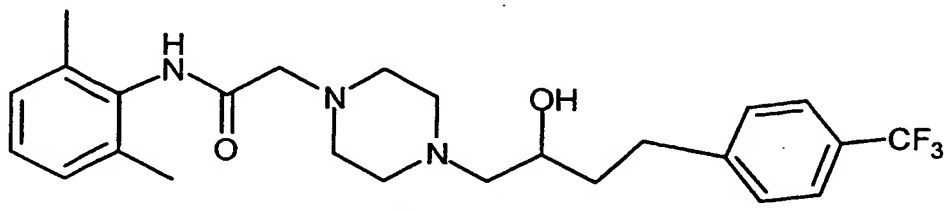
Compound **19B** was prepared in a manner similar to that of compound **16B** substituting 4-t-butylbenzyl chloride for 4-methoxybenzyl chloride. (M + 1) = 452.3



20

N-(2,6-dimethylphenyl)-2-{4-[4-(2-fluorophenyl)-2-hydroxybutyl]piperazinyl}acetamide(20B)

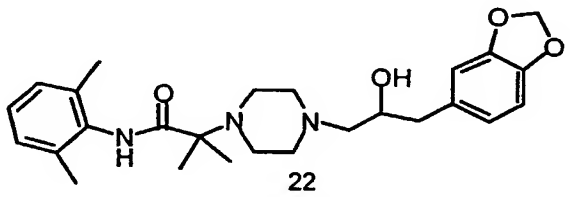
Compound **20B** was prepared in a manner similar to that of compound **16B** substituting 2-fluorobenzyl chloride for 4-methoxybenzyl chloride. (M + 1) = 414.2



21

N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-4-[4-(trifluoromethyl)phenyl]butyl}piperazinyl)acetamide(21B)

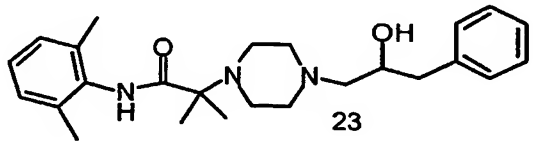
Compound **21B** was prepared in a manner similar to that of compound **16B** substituting 4-trifluoromethylbenzyl chloride for 4-methoxybenzyl chloride. (M + 1) = 464.2



22

2-[4-(3-(2H-benzo[d]1,3-dioxolen-5-yl)-2-hydroxypropyl)piperazinyl]-N-(2,6-dimethylphenyl)-2-methylpropanamide (22B)

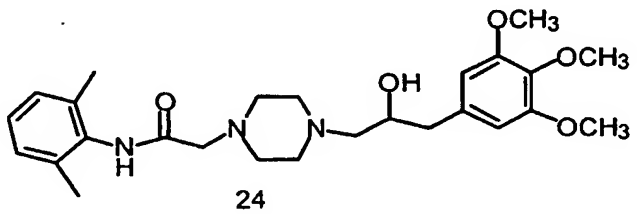
This compound was prepared in a manner similar to that of 7B, substituting 2-chloro-2-methylpropionyl chloride for chloroacetyl chloride in part A. (M+1) = 454.54



23

N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-phenylpropyl)piperazinyl]-2-methylpropanamide (23B)

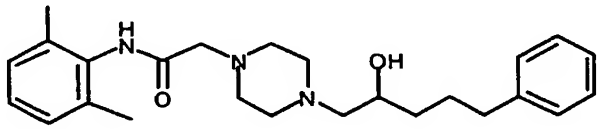
This compound was prepared in a manner similar to that of 7B, substituting 2-chloro-2-methylpropionyl chloride for chloroacetyl chloride in part A and allylbenzene for **8B**. (M+1) = 410.34.



24

N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(3,4,5-trimethoxyphenyl)propyl]piperazinyl}-2-methylpropanamide (24B)

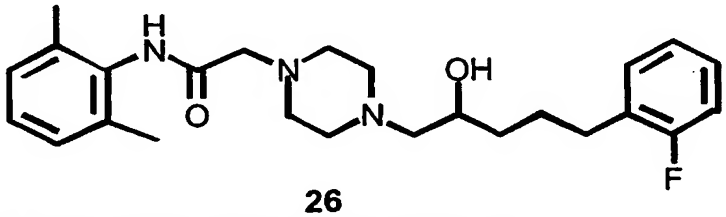
This compound was prepared in a manner similar to that of 7B, substituting 2-chloro-2-methylpropionyl chloride for chloroacetyl chloride in part A and 3,4,5-trimethoxy alkybenzene for **8B**. (M+1) = 472.54



25

N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-5-phenylpentyl)piperazinyl]acetamide (25B)

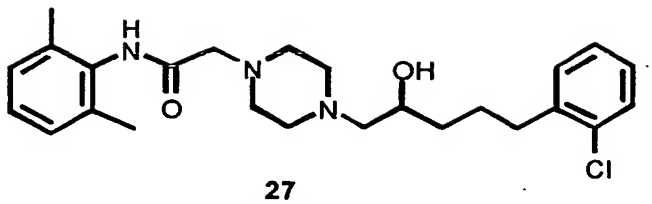
This compound was prepared in a manner similar to that of 16B, substituting phenethyl chloride for 4-methoxybenzyl chloride in part A. (M+1) = 410.4.



26

N-(2,6-dimethylphenyl)-2-{4-[5-(2-fluorophenyl)-2-hydroxy-pentyl]piperazinyl}acetamide(26B)

This compound was prepared in a manner similar to that of 16B, substituting 2-fluorophenethyl chloride for 4-methoxybenzyl chloride in part A. (M+1) = 428.1.



27

N-(2,6-dimethylphenyl)-2-{4-[5-(2-chlorophenyl)-2-hydroxy-pentyl]piperazinyl}acetamide(27B)

This compound was prepared in a manner similar to that of 16B, substituting 2-chlorophenethyl chloride for 4-methoxybenzyl chloride in part A. (M+1) = 444.3

5

Example 6

N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indan-2-yloxypropyl)piperazinyl]acetamide (7C)

Part A.

Synthesis of N-(2,6-dimethylphenyl)-2-chloroacetamide (3C).

2,6-dimethylaniline (9.8g, 81.2 mmol) was dissolved in ether (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) and the reaction mixture was cooled in an ice/water bath. To the cold solution was added chloroacetyl chloride **2C** (9.17 g, 81.2 mmol) dropwise over a period of 2h. The mixture was allowed to warm to RT over 14 h. The mixture was diluted with 100 mL ether and the organic layer was dried over $MgSO_4$, filtered and concentrated to afford compound 3C as a white solid.

Part B.

Synthesis of N-(2,6-dimethylphenyl)-2-piperazinylacetamide (5C).

To a solution of compound **3C** in 100 mL EtOH (5 g, 25.2 mmol) was added compound **4C** (2.1 g, 25.0 mmol) and N,N-diisopropylethylamine (3.2 g, 25.2 mmol). The reaction mixture was refluxed for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (10:1, DCM:MeOH) to afford compound **5C**.

Part C.

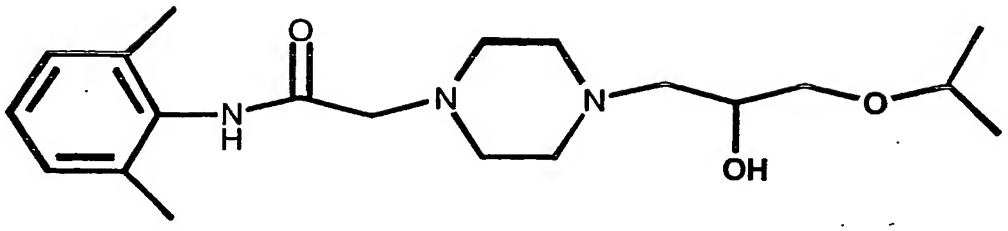
Synthesis of 2-(oxiran-2-ylmethoxy) propane (6C)

To a solution of 60% NaH (0.18g, 4.5mmol) in DMF (10ml) cooled to 0 degrees was added 2-propanol (0.5g, 3,73mmol) in DMF (2ml) dropwise. After stirring for 30minutes epibromohydrin (1.11g, 8.18mmol) in DMF (1ml) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 48 h. The solvent was removed *in vacuo* and the residue was purified using Prep TLC (30:1, DCM:MeOH) to afford compound **6C**.

Part D

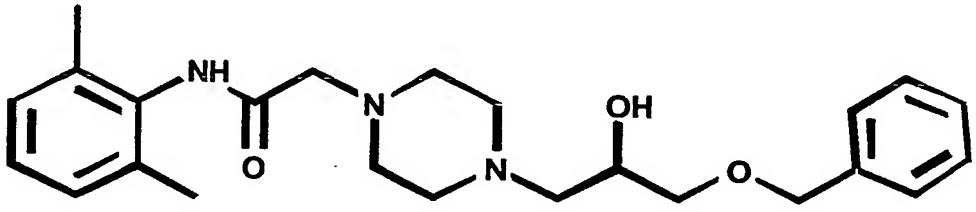
Synthesis of N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indan-2-yloxypropyl)piperazinyl]acetamide (7C)

To a solution of **6C** (0.43g, 2.3mmol) in ethanol(4ml) was added **5C** (0.405g, 1.64mmol). The solution was heated to reflux and stirred for 24 h. Upon completion the solution was concentrated *in vacuo* and purified using Prep TLC (10:1, DCM:MeOH) to yield **7C**. Mass Spectrum (M+1) = 438.36.



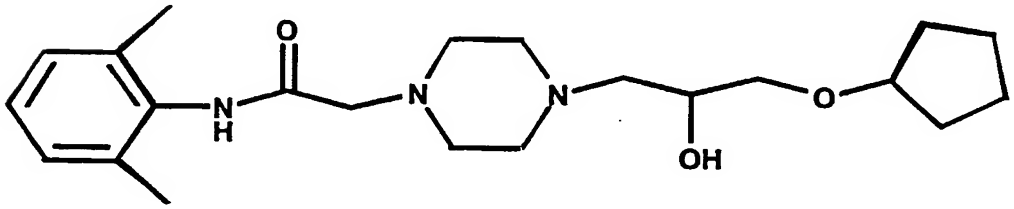
2-({2-[4-(3-isopropoxy-2-hydroxypropyl)piperazinyl]- N-({2,6-dimethylphenyl)acetamide (10C)

Compound **10C** was prepared in a similar manner to compound **7C**, substituting the commercially available glycidyl isopropyl ether for 2-(oxiran-2-ylmethoxy)indane in part D to afford **10C** : Mass spectrum MS (MH+) = 364.37.



N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3 (phenylmethoxy)propyl]piperazinyl}acetamide (11C)

Compound **11C** was prepared in a similar manner to compound **7C**, substituting the commercially available benzyl glycidyl ether for 2-(oxiran-2-ylmethoxy)indane in part D to afford **11C**. Mass Spectrum (M+1) = 412.36.

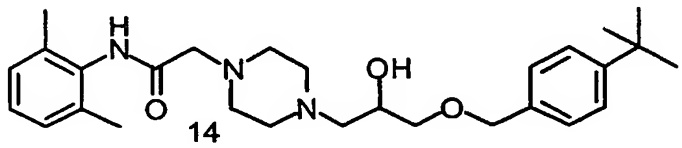


2-({2-[4-(3-cyclopentyloxy-2-hydroxypropyl)piperazinyl]- N-({2,6-dimethylphenyl)acetamide (12C)

Compound **12C** was prepared in a similar manner to compound **7C**, substituting the commercially available cyclopentanol for 2-indanol in part C to afford **12C**: MS (MH+) = 390.

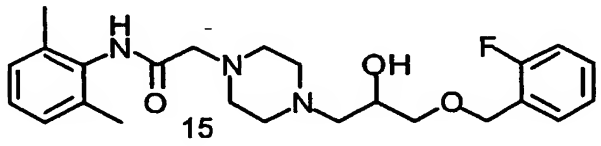
2-({2-[4-(3-cyclohexyloxy-2-hydroxypropyl)piperazinyl]- N-({2,6-dimethylphenyl)acetamide (13C)

Compound **13C** was prepared in a similar manner to compound **7C**, substituting the commercially available cyclohexanol for 2-indanol in part C to afford **13C** - MS (MH+) = 404.



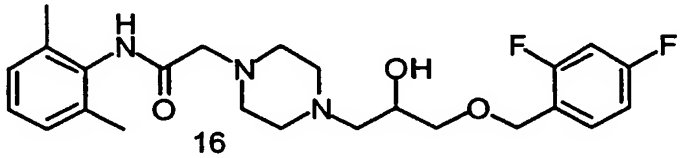
14

2-[4-(3-{[4-(tert-butyl)phenyl]methoxy}-2-hydroxypropyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide (14C): Compound **14C** was prepared in a similar manner to compound **7C**, substituting the commercially available 4-t-bu-benzylalcohol for 2-propanol in part C. MS (M+1) = 468.44



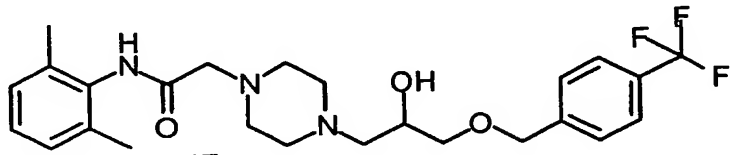
15

N-(2,6-dimethylphenyl)-2-(4-{3-[(2-fluorophenyl)methoxy]-2-hydroxypropyl}piperazinyl)acetamide(15C): Compound **15C** was prepared in a similar manner to compound **7C**, substituting the commercially available 2-fluorobenzylalcohol for 2-propanol in part C. MS (M+1) = 430.39



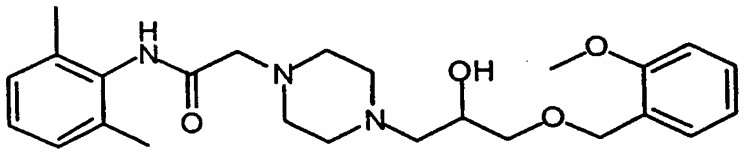
16

2-(4-{3-[(2,4-difluorophenyl)methoxy]-2-hydroxypropyl}piperazinyl)-N-(2,6-dimethylphenyl)acetamide(16C): Compound **16C** was prepared in a similar manner to compound **7**, substituting the commercially available 2,4-difluorobenzylalcohol for 2-propanol in part C. MS (M+1) = 448.38



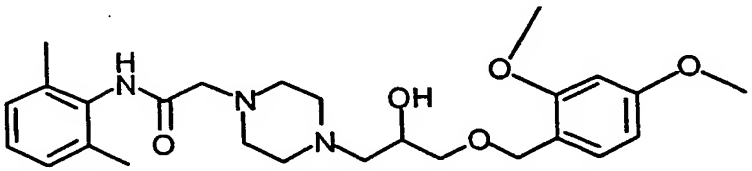
17

N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-{[4-(trifluoromethyl)phenyl]methoxy}propyl)piperazinyl]acetamide (17C): Compound **17C** was prepared in a similar manner to compound **7C**, substituting the commercially available 4-trifluoromethyl-benzylalcohol for 2-propanol in part C. MS (M+1) = 480.37



18

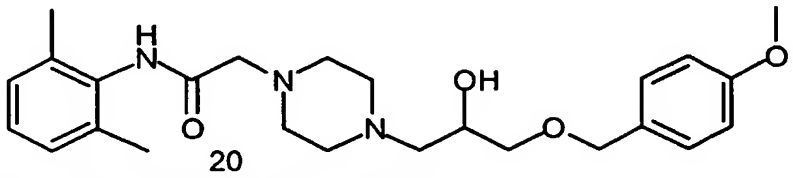
N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(2-methoxyphenyl)methoxy]propyl}piperazinyl)acetamide (18C): Compound **18C** was prepared in a similar manner to compound **7C**, substituting the commercially available 2-methoxy-benzylalcohol for 2-propanol in part C. MS (M+1) = 442.41



19

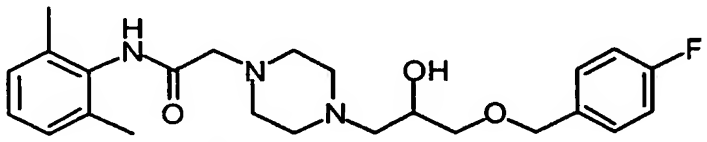
2-(4-{3-[(2,4-dimethoxyphenyl)methoxy]-2-hydroxypropyl}piperazinyl)-N-(2,6-dimethylphenyl)acetamide (19C): Compound **19C** was prepared in a similar manner to

compound 7C, substituting the commercially available 2,4-dimethoxy-benzylalcohol for 2-propanol in part C. MS (M+1) = 472.42



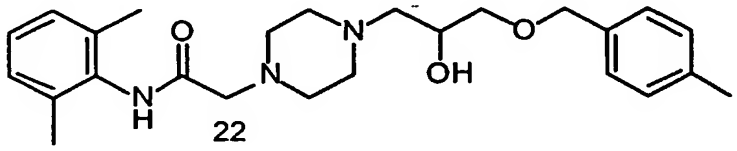
20

N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(4-methoxyphenyl)methoxy]propyl}piperazinyl)acetamide(20C): Compound **20C** was prepared in a similar manner to compound **7C**, substituting the commercially available 4-methoxy-benzylalcohol for 2-propanol in part C. MS (M+1) = 442.42



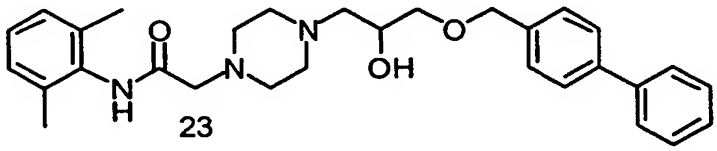
21

N-(2,6-dimethylphenyl)-2-(4-{3-[(4-fluorophenyl)methoxy]-2-hydroxypropyl}piperazinyl)acetamide (21C) Compound **21C** was prepared in a similar manner to compound **7C**, substituting the commercially available 4-fluoro-benzylalcohol for 2-propanol in part C. MS (M+1) = 430.40



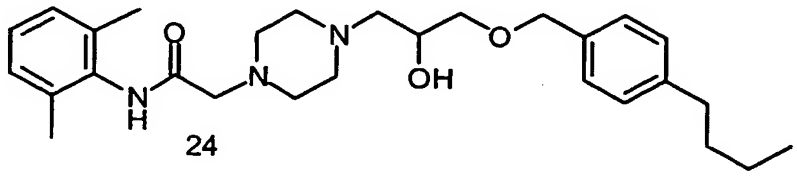
22

N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(4-methylphenyl)methoxy]propyl}piperazinyl)acetamide (22C): Compound **22C** was prepared in a similar manner to compound **7C**, substituting the commercially available 4-methyl-benzylalcohol for 2-propanol in part C. MS (M+1) = 426.41



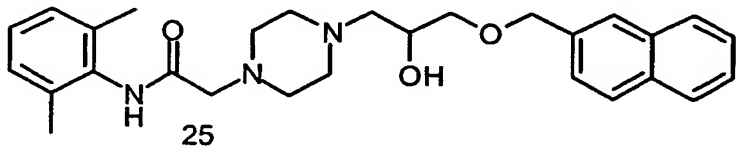
23

N-(2,6-dimethylphenyl)-2-(4-{2-hydroxy-3-[(4-phenylphenyl)methoxy]propyl}piperazinyl)acetamide (23C) Compound **23C** was prepared in a similar manner to compound **7C**, substituting the commercially available 4-phenyl-benzylalcohol for 2-propanol in part C. MS (M+1) = 488.42



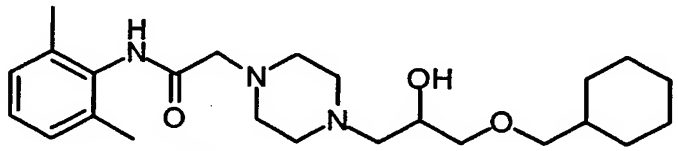
24

N-(2,6-dimethylphenyl)-2-(4-{3-[(4-butylphenyl)methoxy]-2-hydroxypropyl}piperazinyl)acetamide (24C): Compound **24C** was prepared in a similar manner to compound **7C**, substituting the commercially available 4-n-bu-benzylalcohol for 2-propanol in part C. MS (M+1) = 468.45



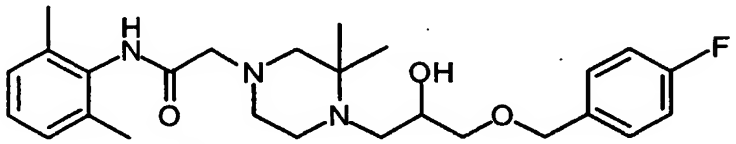
25

N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-naphthylmethoxy)propyl]piperazinyl}acetamide (25C) Compound **25C** was prepared in a similar manner to compound **7C**, substituting the commercially available 2-naphthylmethanol for 2-propanol in part C. MS (M+1) = 462.41



26

N-(2,6-dimethylphenyl)-2-{4-[3-(cyclohexylmethoxy)-2-hydroxypropyl]piperazinyl}acetamide (26C) Compound **26C** was prepared in a similar manner to compound **7C**, substituting the commercially available cyclohexylmethanol for 2-propanol in part C. MS (M+1) = 418.55



27

N-(2,6-dimethylphenyl)-2-(4-{3-[(4-fluorophenyl)methoxy]-2-hydroxypropyl}-3,3-dimethylpiperazinyl)acetamide (27C) Compound **27C** was prepared in a similar manner to compound **7C**, substituting the commercially available 4-fluorobenzylalcohol for 2-propanol in part C and 2,2-dimethylpiperazine for compound 4 part B. MS (M+1) = 458.5

Example 7

Mitochondrial Assays

Rat heart mitochondria were isolated by the method of Nedergard and Cannon (Methods in Enzymol. 55, 3, 1979).

Palmitoyl CoA oxidation – The Palmityl CoA oxidation was carried out in a total volume of 100 micro liters containing the following agents: 110 mM KCl, 33 mM Tris buffer at pH 8, 2 mM KPi, 2 mM $MgCl_2$, 0.1 mM EDTA, 14.7 microM defatted BSA, 0.5 mM malic acid, 13 mM carnitine, 1 mM ADP, 52 micrograms of mitochondrial protein, and 16 microM 1-C14 palmitoyl CoA (Sp. Activity 60 mCi/mmole; 20 microCi/ml, using 5 microliters per assay). The compounds of this invention were added in a DMSO solution at the following concentrations: 100 microM, 30 microM, and 3 microM. In each assay, a DMSO control was used. After 15 min at 30 oC, the enzymatic reaction was centrifuged (20,000 g for 1 min), and 70 microliters of the supernatant was added to an activated reverse phase silicic acid column (approximately 0.5 ml of silicic acid). The column was eluted with 2 ml of water, and 0.5 ml of the eluent was used for scintillation counting to determine the amount of C^{14} trapped as C^{14} bicarbonate ion.

Table 1

Inhibition of mitochondrial fatty acid oxidation using palmitoyl CoA as substrate - % of Control at 3 concentrations.

Compound #	100 μM	30 μM	3 μM
Ranolazine	75%	90%	--
14	--	--	--
7	85%	98%	107%
15	78%	97%	103%
17	89%	98%	100%
16	100%	96%	--
18	17%		
19	-		
22	25%		
23	-		
9B	84%	84%	--
10B	--	--	--
7B	--	--	--
11B	83%	92%	--
12B	42%	95%	
13B	--	--	--
16B	37%		
17B	78%		
18B	78%		
19B	35%		

20B	56%		
21B	56%		
23B	70%		
24B	72%		
10C	100%	97%	--
7C	68%	--	--
11C	79%	--	--
12C	41%	--	--
13C	30%	--	--
14C	21%	-	-
15C	100%	-	-
16C	97%	-	-
17C	35%	-	-
18C	96%	-	-
19C	97%	-	-
20C	100%	-	-
21C	87%	-	-
22C	45%	-	-
23C	12%	-	-
24C	15%	-	-
25C	38%	-	-
26C	70%	-	-
27C	73%	-	-

Example 8

Palmitoyl Carnitine Oxidation

The Palmitoyl carnitine oxidation was carried out in a total volume of 100 microliters containing the following agents: 110 mM KCl, 33 mM Tris buffer at pH 8, 2 mM KPi, 2 mM $MgCl_2$, 0.1 mM EDTA, 0.1 mg/ml of defatted BSA, 0.5 mM malic acid, 3 mM ADP, 52 micrograms of mitochondrial protein, and 43 microM 1-C14 palmitoyl carnitine (Sp. Activity 60 mCi/mmole; 20 microCi/ml, using 5 microliters per assay). The compounds of this invention were added in a DMSO solution at the following concentrations: 100 microM, 30 microM, and 3 microM. In each assay, a DMSO control was used. After 15 min at 30 °C, the enzymatic reaction was centrifuged (20,000 g for 1 min), and 70 microliters of the supernatant was added to an activated reverse phase silicic acid column (approximately 0.5 ml of silicic acid). The column was eluted with 2 ml of water, and 0.5 ml of the eluent was used for scintillation counting to determine the amount of C^{14} trapped as C^{14} bicarbonate ion. The data are presented as % activity of control.

Table 2

Inhibition of mitochondrial fatty acid oxidation using palmitoyl carnitine as substrate - % of Control At 3 concentrations.

Compound #	100 μM	30 μM	3 μM
Ranolazine	63%	98%	--
14	--	--	--
7	95%	102%	109%
15	82%	98%	106%
17	80%	88%	103%
16	64% (8)	--	--
9B	--	--	--
10B	--	--	--
7B	--	--	--
11B	--	--	--
12B	56%	--	--
13B	--	--	--
10C	80%	--	--
7C	--	--	--
11C	--	--	--
12C	--	--	--
13C	--	--	--

Example 9

Metabolic Stability: As a measure of metabolic stability the compounds of this invention were incubated with human liver S-9 microsomal fractions. After, 30 minutes at 37 C, the amount of parent drug remaining was determined using LC-mass spec. The response factors for each compound was determined by establishing a standard curve and using an internal standard during the analysis of the samples. An average of five experiments for percentage of ranolazine remaining at the 30 minute time point is 57%. The compounds of this invention were assayed as described in the protocol below and the percentage of parent remaining was divided by the average % of ranolazine remaining (57%) affording a metabolic stability factor. A compound with a stability number greater than 1.2 has a better stability than ranolazine in the liver S-9 assay. A compound with a stability number between 1.2 and 0.8 has an equivalent stability in the liver S-9 assay. A compound with a stability number less than 0.8 is less stable than ranolazine in the liver S-9 assay.

The purpose of this experiment is to compare the percentages remaining for compounds of this invention with the percentage remaining for ranolazine after 30 minutes of incubation with human liver S9 fractions.

Reagents:

The following reagents were used; Potassium phosphate, 0.5M pH 7.4 (incubation buffer), kept at room temperature; 0.05M $MgCl_2$ kept at 4°C; β-Nicotinamide adenine dinucleotide phosphate, tetrasodium salt, reduced form (NADPH), 0.02M solution in water (~16.6mg/mL) from Sigma Lot # 79H7044 prepared on day of use. 1mM of ranolazine or Compounds 43, 45, 47, 52, 70, 74, 76, 78, and 80 in ACN further diluted to obtain 100μM in 10% ACN; Human S9 stock: 20mg/mL from Gentest.

Procedure:

Incubation mixtures were prepared as follows:

Table 3

Component	Volume per 0.25mL of Incubation Mixture	Final concentration
10μM CVT compounds	25μL	10 μM
$MgCl_2$	25μL	0.005 M
NADPH	25μL	0.002 M
S9	25μL	2 mg/mL
Incubation Buffer	25μL	0.05 M
Water	125μL	----

* 1% organic solvent (acetonitrile) was used in incubation mixture. Generally, 30 incubates were prepared at a time by pre-mixing 0.75 mL of $MgCl_2$, 0.75 mL of incubation buffer, 0.75 mL of NADPH, 3.75 mL of water. Then pipette 200 μL/incubate, add 25 μL of compound being tested, mix, and initiate reaction by addition of S-9.

Combine all components with incubation buffer and re-pipette 200 μL/tube + 25μL of the compound being tested along with 25μL of S-9.

After 5 min of pre-incubation at 37°C, at 0 and 30min after starting the reaction, a 50 μl aliquot of the incubation mixture was removed and added to 100 μL of 9:1 acetonitrile: methanol containing the internal standard.

The mixture was centrifuged and a 100 μL aliquot of the supernatant was diluted in 1mL of solvent C (0.1% Formic Acid in water). Then samples were analyzed for change between the ratio of compound to internal standard at time zero and 30 minutes by LC/MS (injected 10 μL).

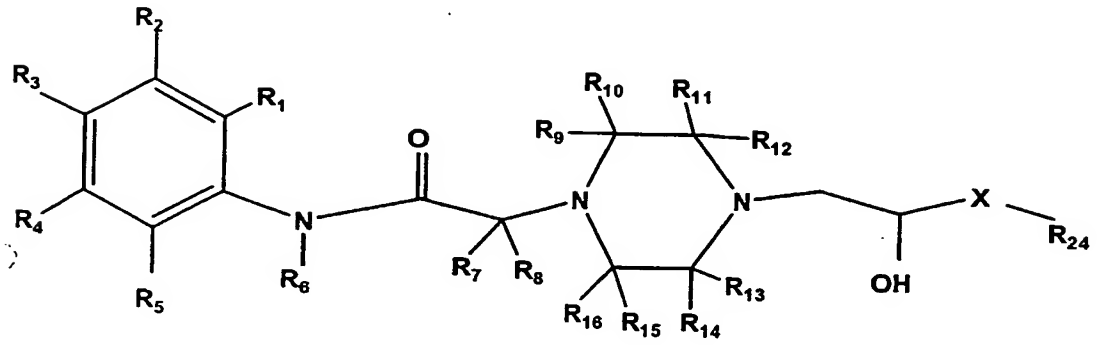
Analytical and Data Calculations:

Samples were analyzed for the starting compounds and potential metabolite/s by LC/MS using an internal standard and an ODS-C18 column with a flow rate of 0.25 ml/min. Following the above procedure resulted in the following relative stability factors as compared to ranolazine for the compounds of this invention as illustrated in Table 4. If a compound is more stable than ranolazine in the liver S9 assay, than the stability factor will be greater than 1.0. If a compound is less stable than ranolazine, than the stability factor will be less than 1.0.

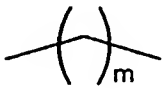
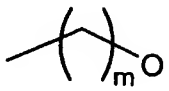
Table 4

Compound #	Liver S9 Stability Factor
Ranolazine	1.0
5	0.45
7	1.51
15	1.20
16	0.15
17	0.45
9B	1.18
10B	1.03
7B	1.46
11B	1.33
12B	1.38
13B	0.10
16B	0.99
17B	0.71
18B	0.68
19B	-
20B	-
21B	-
22B	1.49
23B	0.5
24B	1.05
25B	-
26B	-
27B	-
21C	--
22C	0.61
23C	0.05
24C	0.02
25C	0.01
26C	--
27C	--

1. A substituted piperazine compounds having the following formula:



wherein X is selected from the group consisting of:

 and 

wherein m = 1 or 2 or 3;

R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22} , wherein R_2 and R_3 may join together to form a fused ring system having from three to four carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-;

R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen and $C_{1\text{-}15}$ alkyl;

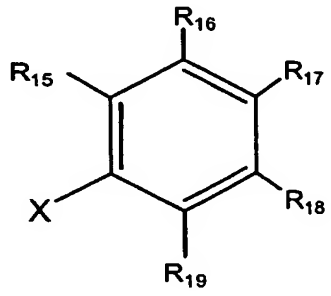
R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, CO_2R_{23}, $CON(R_{23})_2$, $C_{1\text{-}4}$ alkyl, and aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ and aryl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a bridging ring system having from 1 to 4 carbon atoms and wherein R_9 and R_{10} or R_{11} and R_{12} or R_{13} and R_{14} or R_{15}

and R_{16} may join to form a bridging ring system having from 1 to 5 carbon atoms with the proviso that R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are not all hydrogen when R_{24} is phenyl and when X is

R_{22} is selected from the group consisting of C_{1-15} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, and heteroaryl;

R_{23} is selected from the group consisting of H, C_{1-15} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl, CN, -O-C_{1-6} alkyl, and CF_3; and

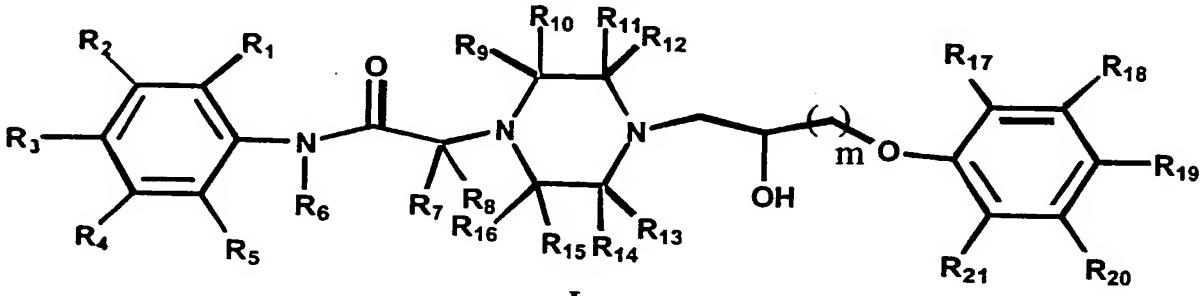
R_{24} is selected from the group consisting of alkyl, cycloalkyl, and fused phenylcycloalkyl wherein the point of attachment is on the cycloalkyl wherein the alkyl, cycloalkyl, and fused phenylcycloalkyl are optionally substituted with from 1 to three substituents selected from the group consisting of halo, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, C_{1-2} alkyl, and aryl wherein the optional aryl substituent is optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, phenyl, CF_3, CN, OR^{20}, and C_{1-6} alkyl and



wherein R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl

substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22};

2. The substituted piperazine compound of claim having the following formula:



I

wherein m = 1 or 2 or 3;

R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22} , wherein R_2 and R_3 may join together to form a fused ring system having from three to four carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-;

R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen and C_{1-15} alkyl;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, CO_2R_{23}, $CON(R_{23})_2$, C_{1-4} alkyl, and aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ and aryl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a bridging ring system having from 1 to 4 carbon atoms and wherein R_9 and R_{10} or R_{11} and R_{12} or R_{13} and R_{14} or R_{15} and R_{16} may join to form a bridging ring system having from 1 to 5 carbon atoms with the proviso that R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are not all hydrogen;

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15}

alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22};

R_{22} is selected from the group consisting of C_{1-15} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, and heteroaryl; and

R_{23} is selected from the group consisting of H, C_{1-15} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl, CN, -O-C_{1-6} alkyl, and CF_3.

3. The compound of claim 2 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, SR_{23}, and $N(R_{23})_2$, wherein R_2 and R_3 may join together to form a fused ring system wherein having from three to four carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-;

R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen and C_{1-8} alkyl;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ and aryl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a bridging ring including from 1 to 4 carbon atoms ; and

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl

substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22}

4. The compound of claim 2 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $SO_2N(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-6} alkyl, C_{2-6} alkenyl, heterocyclyl, and heteroaryl, wherein the alkyl substituent is optionally substituted with 1 substituent selected from the group consisting of CF_3, and OR_{23}, wherein R_2 and R_3 may join together to form a fused ring system having from three to four carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-;

R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen or C_{1-3} alkyl;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, or aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ and aryl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a ring including from 1 to 4 carbon atoms;

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22};

R_{22} is selected from the group consisting of C_{1-15} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, and heteroaryl; and

R_{23} is selected from the group consisting of hydrogen, C_{1-8} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, -O-C_{1-3} alkyl, and CF_3.

5. The compound of claim 2 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $SO_2N(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-6} alkyl, C_{2-6} alkenyl, heterocyclyl, and heteroaryl, wherein the alkyl substituent is optionally substituted with OR_{23}, wherein R_2 and

R_3 may join together to form a fused ring system having from three to four carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-;

R_6, R_7 and R_8 each independently selected from the group consisting of hydrogen and methyl;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen and C_{1-2} alkyl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl;

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, and OR_{23};

R_{22} is selected from the group consisting of C_{1-4} alkyl, aryl, and heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, O-C_{1-3} alkyl, and CF_3; and

R_{23} is selected from the group consisting of H, C_{1-5} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, -OMe, and CF_3.

6. The compound of claim 5 wherein m = 1 or 2.

7. The compound of claim 5 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $SO_2N(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-3} alkyl, C_{2-6} alkenyl, heterocyclyl, and heteroaryl, wherein the alkyl substituent are optionally substituted with OR_{23}, wherein R_2 and R_3 may join together to form a fused ring system having from three to four carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-;

R_6, R_7 and R_8 each independently selected from the group consisting of hydrogen and methyl;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen and C_{1-2} alkyl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl;

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, and C_{1-8} alkyl;

R_{22} is C_{1-4} alkyl; and

R_{23} is selected from the group consisting of hydrogen and C_{1-5} alkyl.

8. The compound of claim 5 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $SO_2N(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-3} alkyl, C_{2-6} alkenyl, heterocyclyl, and heteroaryl, wherein the alkyl substituent is optionally substituted with OR_{23}, wherein R_2 and R_3 may join together to form a fused ring system having from three to four carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-;

R_6, R_7 and R_8 are each hydrogen;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen and C_{1-2} alkyl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl;

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, and C_{1-8} alkyl;

R_{22} is C_{1-2} alkyl; and

R_{23} is selected from the group consisting of hydrogen and C_{1-2} alkyl.

9. The compound of claim 5 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $SO_2N(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-3} alkyl, C_{2-3} alkenyl, heterocyclyl, and heteroaryl, wherein the alkyl substituent is optionally substituted with OR_{23}, wherein R_2 and R_3 may join together to form a fused ring system having from three to four carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-;

R_6, R_7 and R_8 are each hydrogen;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen and methyl, wherein R_9 and R_{10} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl;

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, and C_{1-2} alkyl;

R_{22} is methyl; and

R_{23} is selected from the group consisting of hydrogen and methyl.

10. The compound of claim 5 wherein R_{18}, R_{19}, R_{20}, and R_{21} are each hydrogen, and R_{17} is selected from the group consisting of halo and OR_2.

11. The compound of claim 10 wherein R_{12} is (S)-methyl and R_9, R_{10}, R_{11}, R_{13}, R_{14}, R_{15} and R_{16} are each hydrogen.

12. The compound of claim 10 wherein R_9 and R_{10} together form a carbonyl R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each hydrogen.

13. The compound of claim 10 wherein R_9, R_{10}, R_{11}, R_{12}, R_{15} and R_{16} are each hydrogen and R_{13} and R_{14} together form a carbonyl.

14. The compound of any one of claims 3 to 13 wherein m = 1.

15. The compound of claim 10 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $SO_2N(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-3} alkyl, C_{2-3} alkenyl, N-morpholino, and pyrrolyl, wherein the alkyl substituent is optionally substituted with OH, wherein R_2 and R_3 may join together to form a fused ring system having three carbon atoms, and wherein R_4 and R_5 may join together to form –CH=CH-CH=CH-.

16. The compound of claim 2 wherein m = 1 or 2;

R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-2} alkyl wherein R_{22} is a C_{1-2} alkyl;

R_6, R_7 and R_8 each independently selected from the group consisting of hydrogen and methyl;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl, or R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl with the proviso that R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are not all simultaneously hydrogen and wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join to form a ring including from 1 to 4 carbon atoms.

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, OR_{23}, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, and OR_{23} wherein R_{23} is C_{1-2} alkyl.

17. The compound of claim 16 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, and methyl.

18. The compound of claim 16 wherein R_6, R_7 and R_8 are each hydrogen.

19. The compound of claim 16 wherein R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen and C_{1-2} alkyl, or R_9 and R_{10} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl with the

proviso that R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are not all simultaneously hydrogen and wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join to form a ring having from 1 to 2 carbon atoms.

20. The compound of claim 16 wherein R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen and C_{1-2} alkyl, or R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl.

21. The compound of claim 16 wherein R_9 and R_{10} together form a carbonyl, R_{15} and R_{16} together form a carbonyl or both R_9 and R_{10} together form a carbonyl and R_{15} and R_{16} together form a carbonyl.

22. The compound of claim 16 wherein R_{17}, R_{18}, R_{19}, R_{20} and R_{21} are each independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl and OR^{22} wherein R_{22} is C_{1-2} alkyl.

23. The compound of claim 2 wherein

m = 1;

R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, and methyl;

R_6, R_7 and R_8 are each hydrogen;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl, or R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl with the proviso that R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are not all simultaneously hydrogen and wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{11} may join to form a ring including from 1 to 4 carbon atoms;

R_{17}, R_{18}, R_{19}, R_{20} and R_{21} are each independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl and OR^{22}; and

R_{22} is C_{1-2} alkyl.

24. The compound of claim 23 wherein R_1 and R_5 are each methyl and R_2, R_3, and R_4 are each hydrogen.

25. The compound of claim 23 wherein R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each hydrogen and R_9 and R_{10} together form carbonyl.

26. The compound of claim 23 wherein R_9, R_{10}, R_{11}, R_{12}, R_{15} and R_{16} are each hydrogen and R_{13} and R_{14} together form carbonyl.

27. The compound of claim 23 wherein R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen and methyl.

28. The compound of claim 23 wherein R_9, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each hydrogen and R_{10} and R_{11} together form a ring having from 1 to 4 carbon atoms.

29. The compound of claim 23 wherein R_9, R_{10}, R_{12}, R_{13}, R_{14} and R_{16} are each hydrogen and R_{11} and R_{15} together form a ring having from 1 to 3 carbon atoms.

30. The compound of claim 23 wherein, R_{18}, R_{19} and R_{21} are each hydrogen and R_{17} and R_{18} are each methyl.

31. The compound of claim 23 wherein, R_{17} is $-OCH_3$, and R_{18}, R_{19}, R_{20} and R_{21} are each hydrogen.

32. The compound of claim 23 wherein, R_{17}, R_{18}, R_{20} and R_{21} are each hydrogen and R_{19} is selected from the group consisting of $-OCH_3$, -F, C_{1-4} alkyl and unsubstituted aryl.

33. The compound of claim 2 selected from the group consisting of N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3-oxopiperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3,5-dimethylpiperazinyl}acetamide, 2-{(5S,2R)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-2,5-dimethylpiperazinyl}-N-(2,6-dimethylphenyl)acetamide, 2-{2,5-diaza-5-[2-hydroxy-3-(2-methoxyphenoxy)propyl]bicyclo[4.4.0]dec-2-yl}-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3-oxopiperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-3,3-dimethylpiperazinyl}acetamide, 2-{5-[(2S)-2-hydroxy-3-(2-methoxyphenoxy)propyl](1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl}-N-(2,6-dimethylphenyl)acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-4-(2-methoxyphenoxy)butyl]- piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[4-(4-fluorophenoxy)-2-hydroxybutyl]- piperazinyl}acetamide, 2-(4-{4-[4-(tert-butyl)phenoxy]-2-hydroxybutyl}piperazinyl)-N-(2,6-dimethylphenyl) acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-4-(4-phenylphenoxy)butyl] piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-4-(4-methoxyphenoxy)butyl]- piperazinyl}acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2,6-dimethylphenyl)acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2,6-dichlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-sulfamoylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(5-methoxy-3-(trifluoromethyl)phenyl]acetamide,

2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-indan-5-ylacetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-naphthylacetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-chloronaphthyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2-pyrrolylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-phenylacetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2-chlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2-chloro-4-methylphenyl)acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[2-(1-methylvinyl)phenyl] acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2-methylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[6-methyl-2-(methylethyl)phenyl] acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3-methylthiophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-chloro-2-methoxy-5-methylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[4-(dimethylamino) phenyl] acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2,4-dimethoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3,4-dichlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-chlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3-chlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3,5-dichlorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-methoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-methylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(3-methylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-fluorophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-cyanophenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(4-acetylphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-(2-methoxyphenyl) acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[4-(trifluoromethyl)phenyl] acetamide, 2-{(3S)-4-[(2S)-3-(2-fluorophenoxy)-2-hydroxypropyl]-3-methylpiperazinyl}-N-[4-chloro-3-

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